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Original Communications

THE GLUCOSE TOLERANCE TEST IN CELIAC DISEASE

SIGNIFICANCE OF LOW BLOOD SUGAR CURVES

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IN THE glucose tolerance test, a low blood sugar curve† occurs as an almost constant feature in celiac disease.[1-1c] Because of this observation a low blood sugar curve has come to be accepted as one of the essential laboratory criteria in the diagnosis of this condition. Our data, along with the findings reported in the literature,[1a, 1c, 2] show that such a low curve may be found frequently in sprue, cretinism, disease of the pancreas, or infections, or when malnutrition alone is present. Even a small percentage of normal persons exhibit a low blood sugar curve in the glucose tolerance test.[3]

It has already been established that, in patients with celiac disease, the low blood sugar curve is due to delayed or defective absorption of carbohydrate from the intestine[4, 5, 5a] rather than to a disturbance in intermediary metabolism of carbohydrate[2] or in the renal threshold for glucose.[6] It still remains to determine the mechanism by which this delayed or diminished intestinal absorption takes place, although it has been tacitly assumed that there is an abnormality within the intestinal mucosa itself which is responsible.

In this communication we wish to direct attention to the importance of gastrointestinal motility (emptying of the stomach, peristalsis, and segmentation in the intestine) in the causation of a low blood sugar curve and impairment of absorption from the intestine in celiac disease and other allied conditions.

Because practically no glucose is absorbed from the stomach,[7] it is obvious that any delay or irregularity in the escape of the glucose from the stomach into the duodenum might affect the character of the

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†The curve representing the levels of sugar in the blood at intervals following the oral administration of 0.75 Gm. of glucose per pound of body weight is said to be low when the sugar in the blood does not rise more than 40 mg. per cent above the fasting level.

blood sugar curve. Furthermore, in the normal person, the maximal rise in the blood sugar should be essentially the same whether the glucose is introduced into the stomach or directly into the duodenum by tube.*

In the small intestine, two types of mechanical activity are present which might affect absorption—the onrush peristalsis and the segmenting motions.[9] Glucose is absorbed from the intestine by physiologic activity of the mucosa, and perhaps, to a slight extent, by the physical process of osmosis.[10] In either case, the efficiency of absorption depends upon intimate contact of the mucosa with the intestinal contents which is accomplished by the constant segmenting activity of the gut. Any decrease in this activity would be expected to diminish the efficiency of absorption. The possible influence of increase or decrease of onrush peristalsis is obvious.

METHOD

The role which these mechanical factors play in the origin of the low blood sugar curve and in defective absorption of carbohydrate was determined in our clinical investigations in the following manner. First an oral glucose tolerance test was done to determine the nature of the blood sugar curve. Then the influence of the emptying mechanism of the stomach was eliminated by introducing the glucose directly into the duodenum through a tube. Subsequently, in some of the patients the glucose was again introduced directly into the duodenum while a vigorous activity of the small intestine was maintained by means of mecholyl.† In addition, in many instances, direct observation of the gastrointestinal motility was made simultaneously under a fluoroscope by means of barium sulfate given with the glucose.

The details of the procedure are as follows: In every test, 0.75 Gm. glucose per pound of body weight, made up to a 10 per cent aqueous solution, was used. A fast of at least eight hours was allowed before each test. Samples of blood for sugar analysis were taken before the glucose was given and ½, 1, 1½, 2, 2½, and 3 hours afterward. The sugar in the blood was determined by the Folin-Wu micromethod.[11] Duodenal intubations were done under fluoroscopic control, and the position of the tip of the tube well into the duodenum was assured.

It may be observed that the different types of tests were performed in rapid succession on the same person to avoid variations due to convalescence or changing conditions.

The dosage of mecholyl, when employed, had to be determined by cautious trial in each case. The guiding principle was to give an amount adequate to produce its pharmacologic action without incurring its toxic effects. In general, infants

*This depends upon the fact that the height to which the blood sugar rises is not proportional to the amount of glucose in the intestine after the maximal rate of absorption has been reached. The maximal rise in the blood sugar in infants and children is obtained when from 0.5 to 0.75 Gm. glucose per pound of body weight are given, which utilizes the maximum power of absorption of the intestine.[8]

†Mecholyl (acetyl-beta-methylcholine chloride) is a substance whose action is similar to that produced by stimulation of the parasympathetic nervous system, and it increases intestinal tone, peristalsis, and segmentation. Mecholyl does not improve the emptying of the stomach. Its effects were obtained by introducing the drug, along with, or after, the glucose, directly into the duodenum.

were given 20 mg. mecholyl intraduodenally every one-half hour for three hours without difficulties. Children from 2 to 12 years old were given doses of from 40 to 50 mg. in the same manner. Activity of the intestine was induced by these doses without obtaining deleterious side-effects on the cardiovascular system. The effect on the gastrointestinal tract is most pronounced when mecholyl is administered intraduodenally, and, by this route, the effects on the cardiovascular system are minimized. The toxic effects of mecholyl may be quickly abolished by atropine sulfate. Mecholyl may produce a slight fall in the blood sugar which is insufficient to interfere with the conclusions drawn from our experiments.[12]

RESULTS

A group of infants and children, which included normal, healthy persons and those suffering from celiac disease, fibrosis of the pancreas,[13] infection, cretinism, and malnutrition, were studied by this technique. Summaries of the data are arranged in tabular form in order to indicate the date of the test and the maximal rise* in the blood sugar when glucose was given by the different techniques.

It was found that in normal infants and children the maximal rise in the blood sugar was practically the same (80 to 100 mg. per cent) whether the glucose was administered orally, intraduodenally, or intraduodenally along with mecholyl (Table I).

In five infants and children who showed no evidence of disease and were apparently "normal" and healthy, low blood sugar curves were obtained when glucose was given orally (average rise, 25 mg. per cent). However, when the glucose was given intraduodenally to these persons, the sugar in the blood rose as much as in the normal group (average rise, 80 mg. per cent) (Table II).

Twenty-two patients with celiac disease were studied. When glucose was given orally, the sugar in the blood did not rise above 40 mg. per cent in any patient (average rise, 20 mg. per cent), which is the usual finding in this condition (Tables III and IV).

In sixteen of these patients, when the glucose was given intraduodenally, a normal rise in the sugar in the blood was obtained (average rise, 81 mg. per cent) (Table III). As might be expected, considering this excellent rise, mecholyl given intraduodenally with the glucose produced only a slightly greater rise (average, 131 mg. per cent) which is about the same as occurred with mecholyl in the normal persons. In the remaining six patients the rise in the sugar in the blood was practically as low after intraduodenal administration of the glucose (average rise, 26 mg. per cent) as it had been when they received the glucose orally (Table IV). But, in this group of patients, when mecholyl was given along with the glucose intraduodenally, a considerable improvement in the rise in the blood sugar occurred (average rise, 244 mg. per cent), which was even higher than in the normal group. In Table V are gathered a miscellaneous group of

*See footnote to Table I.

TABLE I

GLUCOSE TOLERANCE TESTS IN NORMAL INFANTS AND CHILDREN

PATIENT NUMBER	AGE	DATE	ORAL, MAXIMAL RISE* (MG. %)	DATE	DUODENAL, MAXIMAL RISE (MG. %)	DIFFERENCE BETWEEN ORAL AND DUODENAL	DATE	DUODENAL WITH MECHOLYL, MAXIMAL RISE (MG. %)	DIFFERENCE ORAL	DIFFERENCE DUODENAL
17	2 yr 6 mo.	7/25/39	71	7/27/39	59	-12				
20	8 mo.	7/20/39	55	7/21/39	96	41				
23	9 mo.	7/14/39	116	7/18/39	89	-27				
2	6 yr.	6/20/38	94	6/14/38	98	4				
9	5 yr.	11/ 9/39	65	11/14/39	121	56				
10	1 yr. 9 mo.	12/ 7/39	116	12/ 9/39	84	-32				
35	9 yr.	4/ 9/40	66	4/10/40	93	27	4/11/40	119	53	26
43	1 yr. 10 mo.	4/17/40	67	4/20/40	107	40	4/21/40	100	23	-7
44	11 mo.	4/17/40	59	4/20/40	37	-22	4/21/40	87	28	50
Average Rise			79		87			102		

*The maximal rise in the blood sugar is the difference between the fasting level and the highest level attained in the course of the glucose tolerance test.

TABLE II

GLUCOSE TOLERANCE TESTS IN "NORMAL" INFANTS AND CHILDREN WITH LOW BLOOD SUGAR CURVES IN THE ORAL TEST

PATIENT NUMBER	AGE	DATE	ORAL, MAXIMAL RISE (MG. %)	DATE	DUODENAL, MAXIMAL RISE (MG. %)	DIFFERENCE BETWEEN ORAL AND DUODENAL	DATE	DUODENAL WITH MECHOLYL, MAXIMAL RISE (MG. %)	DIFFERENCE ORAL	DIFFERENCE DUODENAL
19	7 mo.	7/14/39	29	7/18/39	72	43				
24	1 yr. 4 mo.	10/ 5/39	23	10/10/39	57	34				
34	3 yr. 5 mo.	4/ 9/40	29	4/10/40	56	27				
41	1 mo.	4/17/40	25	4/20/40	103	78	4/21/40	100	75	-3
42	1 yr.	4/17/40	20	4/20/40	111	91				
Average Rise			25		80					

TABLE III

GLUCOSE TOLERANCE TESTS IN INFANTS AND CHILDREN WITH CELIAC DISEASE*

PATIENT NUMBER	AGE	DATE	ORAL, MAXIMAL RISE (MG. %)	DATE	DUODENAL, MAXIMAL RISE (MG. %)	DIFFERENCE BETWEEN ORAL AND DUODENAL	DATE	DUODENAL WITH MECHOLYL, MAXIMAL RISE (MG. %)	DIFFERENCE ORAL	DIFFERENCE DUODENAL
1	9 yr.	5/ 3/38	23	5/16/38	57	34				
5	1 yr. 4 mo.	5/24/38	6	5/28/38	54	48				
6	3 yr.	12/27/38	1	12/31/38	108	107				
8	2 yr.	11/30/38	13	12/ 6/38	48	35				
10	1 yr. 9 mo.	6/27/38	24	7/21/38	71	47				
13	7 yr. 6 mo.	5/ 8/39	34	5/12/39	125	91				
15	5 yr.	3/ 8/39	37	3/ 9/39	47	10				
22	2 yr. 6 mo.	5/ 4/38	22	5/17/38	55	33				
22	3 yr. 4 mo.	3/25/40	32	4/ 1/40	106	74				
9	5 yr.	2/28/40	23	3/ 5/40	55	32				
25	1 yr.	3/ 6/40	14	3/19/40	70	56				
25	1 yr. 1 mo.	4/10/40	10	4/12/40	47	37	4/18/40	143	133	96
26	4 yr. 6 mo.	3/16/40	36	3/19/40	58	22				
26	4 yr. 7 mo.	4/17/40	19	4/24/40	80	61				
28	1 yr. 1 mo.	11/ 7/39	17	11/10/39	58	41				
28	1 yr. 3 mo.	2/ 6/40	25	2/ 8/40	146	121	2/15/40	183	158	37
31	4 yr. 6 mo.	5/11/39	21	5/17/39	147	126				
31	4 yr. 11 mo.	10/26/39	30	10/28/39	74	44				
31	5 yr.	11/ 7/39	10				11/21/39	85	75	
36	8 yr. 2 mo.	4/ 1/40	37	4/ 5/40	111	74	4/11/40	114	77	3
38	1 yr. 1 mo.	4/ 8/40	35	4/15/40	117	82				
40	1 yr. 2 mo.	2/24/40	24	3/21/40	71	47				
Average Rise			22		81			131		

*We have considered the "celiac disease" syndrome as including the characteristic wasting; distention of the abdomen; large, pale, putrefactive, "fatty" stools; excess fat in the feces by chemical analysis; clumping of barium in the small intestine; and "flat" glucose tolerance curve.

We have observed that the features of the "celiac disease" syndrome may appear as a result of a variety of disorders which interfere with the proper utilization of food substances. Thus, these criteria cannot be taken as pathognomonic signs of a particular disease.

The patients in Tables III and IV suffered from celiac disease as it is commonly understood. Their health improved on treatment with a celiac diet, and no other underlying disease was found which could account for their symptoms.

TABLE IV

GLUCOSE TOLERANCE TESTS IN INFANTS AND CHILDREN WITH CELIAC DISEASE

PATIENT NUMBER	AGE	DATE	ORAL, MAXIMAL RISE (MG. %)	DATE	DUODENAL, MAXIMAL RISE (MG. %)	DIFFERENCE BETWEEN ORAL AND DUODENAL	DATE	DUODENAL WITH MECHOLYL, MAXIMAL RISE (MG. %)	DIFFERENCE ORAL	DIFFERENCE DUODENAL
7	3 yr.	12/ 2/38	20	12/15/38	17	-3				
12	2 mo.	9/22/38	20	9/24/38	35	15				
14	5 yr. 6 mo.	6/23/39	7	6/29/39	39	32				
16	8 mo.	2/21/39	3	3/ 1/39	15	12				
18	2 yr. 11 mo.	6/19/39	15	7/12/39	10	-5				
32	1 yr. 9 mo.	11/13/39	25	11/17/39	26	1	11/23/39	74*	49	48
32	1 yr. 10 mo.						12/19/39	407		
9	5 yr. 2 mo.	4/23/40	32	4/24/40	38	6	4/18/40	250	218	212
Average Rise			18		26			244		

*Mecholyl subcutaneously.

TABLE V

GLUCOSE TOLERANCE TESTS IN MISCELLANEOUS CONDITIONS AFFECTING INFANTS AND CHILDREN

PATIENT NUMBER	AGE	DATE	ORAL, MAXIMAL RISE (MG. %)	DATE	DUODENAL, MAXIMAL RISE (MG. %)	DIFFERENCE BETWEEN ORAL AND DUODENAL	DATE	DUODENAL WITH MECHOLYL, MAXIMAL RISE (MG. %)	DIFFERENCE ORAL	DIFFERENCE DUODENAL
					Fibrosis of the Pancreas					
29	10 mo.	1/16/40	46	1/11/40	103	57				
30	1 yr. 1 mo.	6/14/39	26	7/20/39	27	1				
	Average Rise		36		65					
					Malnutrition					
3	5 yr.	2/24/38	23	3/ 3/38	101	78				
11	1 yr. 4 mo.	8/ 9/38	24	8/17/38	38	14				
21	2 yr.	7/25/39	8	8/ 3/39	87	79				
46		5/13/40	37	5/14/40	53	16	5/16/40	72	35	19
	Average Rise		23		70					
					Infection					
33	5 mo.	4/ 8/40	25	4/23/40	59	34	4/27/40	85	60	26
					Cretinism					
4	6 mo.	8/ 5/38	12	7/ 8/38	38	26				

allied conditions in which the blood sugar curve was low when the glucose was given orally, whereas a normal rise in the blood sugar was frequently obtained simply by introducing the glucose directly into the duodenum.

FLUOROSCOPIC STUDIES

Valuable evidence of alterations in gastrointestinal motility in celiac disease and allied conditions was obtained by direct fluoroscopic observation of the behavior of the gut by means of an opaque barium meal.

We were able to follow the movements of the bowel in the same fashion as in the original classic investigations of gastrointestinal motility of Cannon,[9] and we observed the activities of the stomach and the small intestine which he described.

As an added feature, we frequently combined fluoroscopic observations and glucose tolerance tests by giving a meal of barium sulfate suspended in glucose solution.* Control observations on normal and pathologic subjects revealed that the same results were obtained both as regards the blood sugar curves and the motility, whether the barium sulfate and glucose were given separately or mixed together in our standard test meal.

The sequence of events we observed by combining glucose tolerance tests with fluoroscopic examination was consistent in these groups of patients and may be described in outline.

In the normal infants and children there was a steady discharge of the barium meal out of the stomach from the time it was ingested until two or three hours later when the stomach was empty. The barium meal, as it passed through the duodenum and jejunum, assumed a rather feathery appearance, and active onrush peristalsis and segmenting movements could be seen. In the ileum the more smooth-walled appearance of the bowel was seen, and again active peristalsis and segmentation could be observed throughout the gut. The movements were regular and rhythmical, and this type of activity was apparent in several portions of the intestine at each observation. The importance of this "kneading" action in promoting effective absorption was most impressive. The nature of the emptying of the stomach and the movements in the small intestine coincided with the character of the blood sugar curves which were obtained simultaneously, i.e., a high rise with return approximately to the fasting level within three hours. The action of mecholyl accentuated these movements, giving the appearance of a slightly more vigorous activity, corresponding to the slight additional rise in the glucose tolerance test.

*The meal was standardized so that each patient received 1.5 Gm. barium sulfate per pound of body weight, along with 0.75 Gm. glucose per pound of body weight. Water was added to make the final suspension 10 per cent glucose and 20 per cent barium sulfate.

In the cases of the infants and children with low blood sugar curves, whether from celiac disease or the other conditions, the gastrointestinal motility as observed by fluoroscopy consistently revealed "sluggish" behavior. The entire barium meal frequently remained in the stomach for over three hours, the duration of the usual oral glucose tolerance test. Naturally, the blood sugar curves obtained at the same time were low because no appreciable quantity of glucose is absorbed from the stomach. Even if delivery of the barium meal from the stomach began sooner, the barium escaped irregularly and in small amounts. There was usually as much as 50 per cent of the barium meal remaining in the stomach three hours after its ingestion.

Furthermore, the pattern of movements and disposition of the barium meal in the intestine was characteristically different from the normal. The jejunum and ileum were dilated as though they lacked tone. The segmenting action either was completely absent or occurred at infrequent intervals in isolated areas of the bowel. Even when segmentation could be seen, it was slow and feeble. As a result, the barium meal tended to collect in large inactive clumps in the dilated bowel which had lost its normal feathery contour in the jejunum. This is the picture which has been so frequently described as the "clumping" characteristic of celiac disease.[1a] The sluggish action of the gastrointestinal tract and the apparent loss of tone of the intestine offer an adequate explanation of this roentgenologic appearance, and, as would be expected, it is not found exclusively in celiac disease, but may be present in any condition affecting gastrointestinal motility in this manner. The glucose tolerance tests performed at the same time as these fluoroscopic observations reflected, by low blood sugar curves, the inefficient mechanical action of the bowel.

The dramatic effects of mecholyl on the behavior of the intestine in these persons were interesting and significant. Within a few minutes after the administration of the drug, the picture of "clumping" of the barium meal into inactive masses in the dilated bowel was completely transformed by the action of the mecholyl. A vigorous segmental and peristaltic activity commenced within from one to three minutes after the drug was given. The tone returned to the bowel, and the lumen became normal in size. The appearance became normal throughout the small intestine; even the feathery character of the jejunum returned. Along with these improvements in the motility, an increased rise in the blood sugar curve occurred. In fact, in every patient in whom this experiment could be attempted, a normal rise in the blood sugar was obtained.

Several patients in whom fluoroscopic examination showed defective intestinal motility and who also had low glucose tolerance tests were re-examined after they had recovered from their affections. When

they had convalesced, the oral glucose curves became normal, and the gastrointestinal motility, as observed under the fluoroscope, showed a corresponding return to normal activity.

DISCUSSION

The evidence presented supports the hypothesis that the character of the blood sugar curve in the glucose tolerance test is affected by the gastrointestinal motility, including emptying of the stomach and peristalsis and segmentation in the small intestine. The implications of impaired activity of the bowel, in so far as absorption is concerned, are self-evident.

When a normal rise in the blood sugar was obtained simply by introducing the sugar into the duodenum, a delayed emptying of the stomach may be held responsible for the low oral curve. If mecholyl was required, in addition to intraduodenal administration of glucose, to produce a normal rise in the blood sugar, then the peristalsis and segmentation of the small intestine must also have been inactive. Whenever both these defects in gastrointestinal motility were corrected by introducing mecholyl and glucose into the duodenum, the absorption of glucose became normal.

This indicates that there is no specific defect in absorption of carbohydrate by the intestinal mucosa in celiac disease or in these other allied conditions which showed low blood sugar curves in the glucose tolerance test. The low blood sugar curves seem to be merely a reflection of the inactivity in gastrointestinal motility, with consequent inefficient absorption despite a normal intestinal mucosa. This information brings into bold relief the difficulty of interpretation of a glucose tolerance test which depends upon gastrointestinal motility. It makes it clear that the glucose tolerance test cannot be expected to be diagnostic of a particular condition, such as celiac disease, but rather will be affected by any of the numerous conditions altering gastrointestinal motility.

The paucity of pathologic changes found on histologic examination at necropsy in the gastrointestinal tract of patients with celiac disease has made it seem plausible that some functional derangement would better account for the defective absorption in this condition.[1a] As far as carbohydrate is concerned, the impaired mechanical function seems to be an adequate explanation for the defective absorption. It remains to determine whether other functional alterations account for impairment of absorption of fat or protein.

CONCLUSIONS

In the glucose tolerance test the low blood sugar curve which occurs in celiac disease and other allied conditions is a result of diminished intestinal absorption.

This defect in absorption of carbohydrate is dependent upon the inactivity of the gastrointestinal motility which we have described.

There is no specific defect in absorption of glucose inherent in the mucosa in celiac disease.

The alteration in gastrointestinal motility offers an explanation for the appearance, in the small intestine, of "clumping" of the barium meal, which has been described in roentgenograms.

It should be emphasized that the low blood sugar curve and the "clumping" of barium in roentgenograms are not diagnostic of celiac disease. As we have shown, these features may be present in several conditions in which the activity of the gastrointestinal tract is diminished.

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PRIMARY CARCINOMA OF THE LIVER, WITH BANTI'S SYNDROME

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THE present report concerns a case of primary carcinoma of the liver in a 6-year-old female child with progressive splenomegaly, together with anemia, a known leucopenia of three and one-half years' duration, severe gastric hemorrhage, terminal jaundice, and ascites. The justification for reporting the case lies in the rarity of such a combination of symptoms, closely simulating Banti's syndrome. A survey of the literature on primary carcinoma of the liver associated with other diseases, in children, fails to disclose a single case with similar symptom complex.

The incidence of primary carcinoma of the liver is rare, and particularly so in childhood. Ordinarily it is not considered as a possibility and usually is discovered only at post-mortem. The authenticity of a certain number of reported cases is doubtful, as suggested by Steiner (1938) who, after having reviewed 105 cases of the disease occurring in children, concluded that only sixty-five of them gave evidence sufficient to justify the diagnosis.

Wheeler (1909), Boyce and McFetridge (1934), and Steiner (1938) all agreed that the clinical manifestations of the disease were not at all characteristic and were dependent largely upon the nature and extent of the neoplastic process in each particular instance. However, in all cases, there was uniformity in the speed with which the disease proceeded to its fatal conclusions.

Castle (1914) and Winternitz (1916) reported cases of portal thrombosis caused by the presence of tumor tissue. Steiner (1938) found secondary growths in 27.7 per cent of cases in children, as compared with 66 per cent found by Eggel (1901) in adult cases. Karsner (1911) states that extrahepatic metastases are more widespread than is usually believed. The intrahepatic extensions, however, are also frequent.

It is of interest to note with Steiner (1938) and Castle (1914) the occurrence of an enlarged liver in the majority of cases. According to Greene (1939), cirrhosis of the liver has been found less common in children than in adults. Strong and Pitts (1930) are of the opinion that an early fixation of the liver pulls the enlarged organ upward more frequently than downward, since less resistance is offered by the diaphragm and lungs than by the ascitic fluid in the peritoneal cavity.

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Consequently, the enlargement of the liver is often not noted at once or is entirely overlooked. Greene (1939) observed in adults a palpable liver in 48 per cent of the cases and an enlarged spleen in 34 per cent. Tull (1932) found splenomegaly in two-fifths of the cases he studied (52 out of a total of 134 cases).

The cases reported under such titles as "Thrombophlebitis of the Veins of the Portal System," "Splenic Anemia," "Splenomegaly," and "Banti's Disease or Syndrome" include many cases rather similar to those described by Smith and Howard (1927), in which hematemesis and splenomegaly occurred early in life. The size of the enlarged spleen decreased after hemorrhage and increased with restoration of the blood volume. The blood picture remained practically normal, except, of course, for a secondary anemia immediately following hemorrhage. Severe symptoms of ascites, if it occurred at all, came on late in the disease.

The syndrome described by Banti (1894) consisted of splenomegaly, anemia, leucopenia, and hepatic cirrhosis. The decreased size of the spleen after hemorrhage, followed by an increase in size, as described by Smith and Howard (1927), is common in thrombophlebitis of the splenic vein, but not so in Banti's disease. Many authors do not recognize thrombophlebitis of the splenic and portal veins to be essential to Banti's syndrome. Warthin and Dock (1904) were the first to suggest that obstruction of the portal circulation, due to thrombophlebitis of the portal or splenic vein, caused splenomegaly. Wallgren (1927) believes that obstruction to the venous return may result either from selerosis of the vessel walls accompanying phlebitis, or from retraction of adhesions about the vein following plastic peritonitis, or from pressure from without. Warthin (1910) was convinced that, except for secondary anemia and leucopenia, there is absolutely nothing in the clinical or pathologic picture that can differentiate the cases of splenic or portal thrombosis from cases of Banti's disease or splenic anemia. Secondary anemia and leucopenia have been demonstrated in cases of splenic thrombosis. If Banti's disease, thrombophlebitis of the splenic vein, and splenic anemia all have a common and identical pathologic process, it is possible that the Smith-Howard-Wallgren syndrome may also be regarded as only a particular manifestation of the same group of diseases.

CASE REPORT

M. H., a female identical twin, was born on March 24, 1933. Her twin sister died of an unknown disease three weeks after birth. At 2½ months of age the patient was taken to a pediatrist because of inability to thrive on various formulas, and a persistent cough, together with failure to gain weight. At this examination the spleen was palpated 1 inch below the left costal margin. No hepatomegaly, adenopathy, or jaundice was observed. Changes in formula, as well as introduction of other foods, were poorly tolerated.

The patient entered Michael Reese Hospital* on Aug. 5, 1935, for treatment of a fracture of the left femur, caused by falling downstairs. Physical examination at this time revealed a markedly malnourished and mentally retarded 2½-year-old child. She would pull hair from her head constantly and eat it, eventually destroying all her hair in this manner. The enlarged spleen was now, approximately two years after the first examination, found to be elongated downward, firm to touch, but freely movable. The liver was not enlarged, and there was no icterus or ascites. Temperature ranged between 100 and 102° F. The left femur showed an angulated deformity at the junction of the middle and upper thirds of the shaft. There were scattered petechiae on the skin of the left forearm. An ophthalmoscopic examination revealed waxy pale, sharply outlined disks with a "salt-and-pepper" appearance of the entire fundi in both eyes. An open reduction of the fractured femur, with application of the cast, resulted in a rapid and satisfactory healing.

Laboratory examinations were negative as to bacteriology, serology, and skin tests (Dick, Schick, and Mantoux). The nonprotein nitrogen (35 mg.), inorganic phosphorus (3.3 mg.), and cholesterol (236 mg.) of the blood were considered to be within normal range. Blood counts revealed moderate anemia and distinct leucopenia (Table I).

TABLE I

BLOOD STUDIES

DATE	RED BLOOD COUNT (MILLIONS)	HEMOGLOBIN (GM. %)	PLATELETS (PER C.MM.)	SEDIMENTATION RATE (% 1 HOUR)	PROTHROMBIN TIME (SECONDS)	ICTERIC INDEX (MURPHY UNITS)
8/ 6/35	3.66	8.25	—	—	—	—
8/15/35	3.69	8.25	—	—	—	—
9/21/38	2.99	7.25	—	—	—	—
7/28/39	2.92	7.6	80,000	50	24	12
7/30/39	3.24	8.5	40,000	46	24	10
8/ 8/39	2.91	8.7	70,000	50	19	12
8/18/39	2.01	7.0	90,000	56	24	10

LEUCOCYTE AND DIFFERENTIAL COUNTS

DATE	TOTAL WHITE BLOOD CELLS (PER C.MM.)	POLYMORPHONUCLEAR CELLS (%)	LYMPHOCYTES (%)	MONOCYTES (%)	EOSINOPHILES (%)	BASOPHILES (%)	PLASMA CELLS (%)
8/ 6/35	3,550	77	31	1	1	0	0
8/15/35	3,450	54	42	2	1	1	0
9/21/38	2,260	52	44	2	2	0	0
7/28/39	2,100	67	22	2	7	0	2
7/30/39	1,600	59	26	7	5	1	2
7/31/39*	7,500	70	15	4	9	0	2
8/ 8/39	1,900	51	28	13	7	0	1
8/18/39	1,900	60	30	5	4	0	1

*Thirty minutes after injection of 0.5 c.c. adrenalin.

A diagnosis of splenomegaly, probably Banti's disease, was made, and splenectomy was advised. But, because the father objected to an operation, the child was discharged on Sept. 5, 1935.

The patient was not observed again until Sept. 21, 1938, at which time she was seen by one of us (V. B. W.). The complaints were listed as follows: periodic vomiting of blood, heaviness on the left side, vomiting of food, alternating diarrhea and constipation with black stools, loss of appetite, failure to gain, "pulls hair

*Permission was obtained to use data collected at the Michael Reese Hospital.

from head and eats it,'' stumbling, inability to learn, weakness, muddy yellow skin, heavy breathing upon exertion, and a very large abdomen which fluctuated in size.

Physical examination at this time revealed a dwarfed 6-year-old female child, weighing 27 pounds, with a standing height of 35.5 inches, who gave evidence of pronounced asthenia and fatigue. Her face wore an expression of weakness and anxiety. The entire body was emaciated, and all skin areas had a sallow, dry, bronzed appearance. The mucous membranes throughout were pale and gray. Percussion demonstrated a diaphragm up to the third inetrspace on the left side. The abdomen was very large, the skin over it being pulled so tightly that it glistened; the dilated superficial veins varied in width from 5 to 8 mm. (Fig. 1). The liver edge was not felt; succussion sounds were demonstrated. The spleen, filling the entire left and the upper two-thirds of the right abdominal cavity, was firm in consistency and smooth to touch, while the notch was well outlined below the level of the umbilicus. Repeated blood counts revealed an increasing anemia and leucopenia (Table I). A diagnosis of Banti's syndrome was made, and hospitalization was advised but refused.

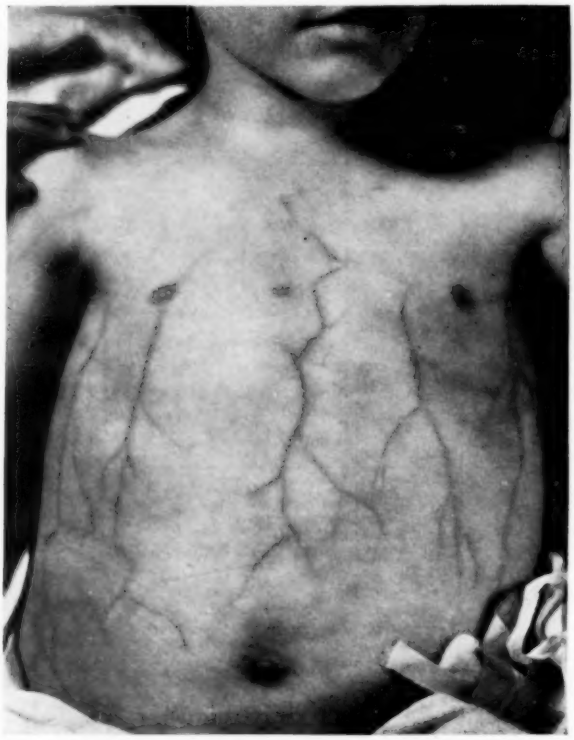

Fig. 1.—Photograph of patient made on Aug. 3, 1939, showing dilated superficial veins of the trunk.

Periodic bouts of ascites and hematemesis continued, however, and finally on July 26, 1939, the child was brought to the Bobs Roberts Memorial Hospital of the University of Chicago. The complaints were the same as recorded on Sept. 21, 1938,

with the addition of "bruised spots" on the body. Physical findings were again identical to those noted previously, but with the addition of petechiae and ecchymotic areas on various parts of the body.

Complete blood counts, sedimentation rates, prothrombin time, and icteric index determinations are summarized in Table I. The coagulation time, by the method of capillary tube, was 3.5 minutes; a fragility test gave an initial hemolysis at 0.44 per cent of sodium chloride solution and a complete hemolysis at 0.30 per cent. A sternal marrow puncture revealed hyperplastic myeloid elements, numerous normoblasts, and an abundance of megakaryocytes. A splenic puncture showed essentially the same picture as that of the peripheral blood. No Gaucher or other lipoid cells and no megakaryocytes, normoblasts, or immature myeloid elements were found in the splenic puncture smears. The hippuric acid excretion was 17 per cent in four hours after ingestion of 3 Gm. of sodium benzoate. The nonprotein nitrogen (21 to 31 mg.), cholesterol (178 mg.), and total serum protein (5.6 Gm.) of the blood were slightly lower than those found in 1935. An oral glucose tolerance test demonstrated a typical diabetic curve, while an intravenous test was normal (Fig. 2). Bacteriology and serology were negative. Roentgenograms of the chest revealed enlargement of the heart on both borders and increased vascular markings in both the upper and lower lobes of the lungs.

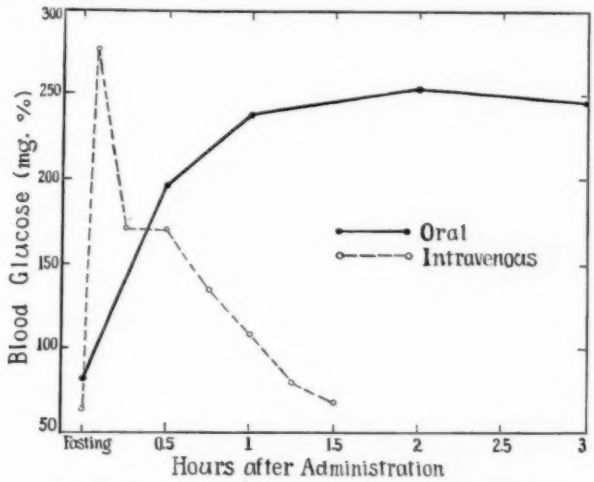

Fig. 2.—Glucose tolerance tests (oral and intravenous).

The clinical course definitely indicated an unfavorable prognosis, and splenectomy was finally decided upon. Inasmuch as the patient was considered a poor surgical risk because of increasing anemia, precautionary measures were taken by repeated intravenous injections of normal saline and blood transfusions both before and during the operation, which was performed under general anesthesia. A moderate amount of bleeding occurred during the section of the pedicle. Approximately one-half gallon of ascitic fluid was removed from the peritoneal cavity. The liver was inspected on all surfaces and was found to be slightly enlarged with a granular-appearing surface.

Eight hours following the operation the patient suddenly developed a temperature of 40.6° C. Respiration, rapidly becoming gruntlike and shallow, was accompanied

by pronounced flaring of the nasal alae and a hacking nonproductive cough. Râles, dullness, bronchial breathing, and bronchophony were noted over the right lobe posteriorly. As the child was being placed in the oxygen tent, she struggled violently; this was followed by projectile vomiting of a large amount of fresh blood. She died while a transfusion was being administered.

NECROPSY PROTOCOL

The autopsy, performed nine hours after death, led to the following anatomic diagnoses: (1) advanced cirrhosis of the liver; (2) hemorrhage into the gastrointestinal tract from esophageal varices; (3) splenomegaly; (4) hemorrhagic ascites; (5) primary carcinoma of the liver with intrahepatic metastases; (6) early bilateral bronchopneumonia; (7) fatty degeneration of the heart and kidneys; (8) emaciation; (9) generalized anemia; (10) hyperplasia of bone marrow; (11) hair ball in the stomach; and (12) fibrous pleural adhesions.

The external appearance of the body resembled that of a much younger child. The abdomen contained about 800 c.c. of thin bloody fluid, but the peritoneal surfaces were smooth and glistening. Numerous sutures and ligatures were noted in the region that had contained the previously removed spleen. No obvious bleeding points or clotted blood were found. The stomach and intestines were greatly distended. The liver was small and lay far above the costal margin. Throughout its length the esophagus showed numerous anastomosing varices and a superficially eroded mucosa. No large bleeding areas were found, and the varices were not thrombosed. The lungs contained evidence of early pneumonia in both lower lobes and in the upper lobes posteriorly.

The liver was greenish-yellow in color and small in size, weighing only 440 Gm. Its capsule was slightly thickened and its surface nodular. The dome of the right lobe contained a tumor nodule, measuring 5 by 5 by 4 cm. and projecting nearly 1 cm. above the surface of the surrounding liver tissue. The tumor was poorly circumscribed, unencapsulated, firm in consistency, and the surface made by cutting through the nodule revealed areas varying in color from yellow to pearly gray. Adjacent to this main nodule, whose margins were slightly irregular, were small metastases, measuring up to 5 mm. The only other metastasis noted was on the inferior surface of the right lobe of the liver, a nodule about 1 cm. in size projecting above the surface of the organ. The liver itself was slightly flabby, but it cut with increased resistance to reveal a surface mottled by yellow and green. Normal lobular markings were obliterated, the hepatic tissue being divided irregularly by connective tissue into small lobular-sized areas.

The spleen, surgically removed before death, was greatly enlarged, measuring 20 by 10 by 3.5 cm. The serosal surface was smooth. Cut sections showed a meaty surface with numerous large blood vessels. The Malpighian bodies were not distinct; there were no metastases. The organ weighed 229 Gm., and approximately one-half gallon of blood-tinged ascitic fluid accompanied the specimen.

The heart, aorta, and other vessels were normal in configuration. The epicardial fat showed serous atrophy. The myocardium was firm and reddish-brown in color. Except for the digital half of the splenic vein and the periumbilical veins, both of which contained recent red thrombi, no abnormalities were found in any of the vessels examined. The portal system as a whole was free from obstruction.

The adrenals, small and pale, appeared to consist mostly of pale yellow cortex. The lymph nodes were conspicuous because of the marked resorption of body fat, but they gave no evidence of metastases. The skeleton revealed no abnormalities in configuration. The bone marrow from the sternum, lumbar spine, third dorsal vertebra, and right seventh rib was dark red in color and rather fluid in appear-

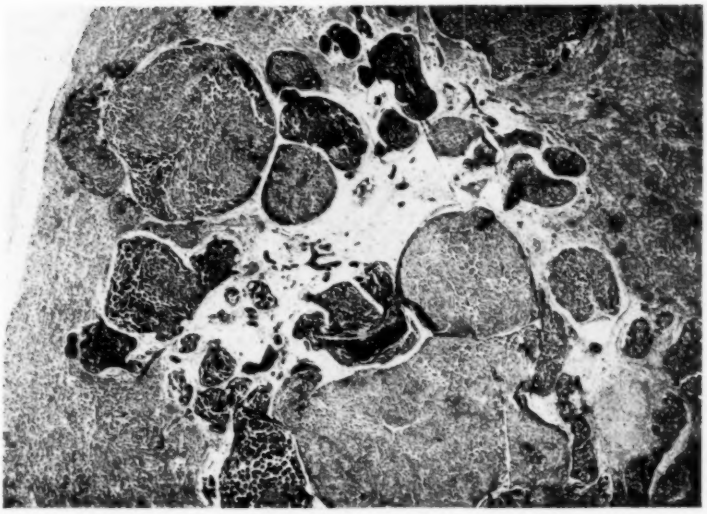

Fig. 3.—Photomicrograph of liver section through neoplastic nodule, showing bundles and cords of malignant cells separated by young connective tissue strands. (×12.)

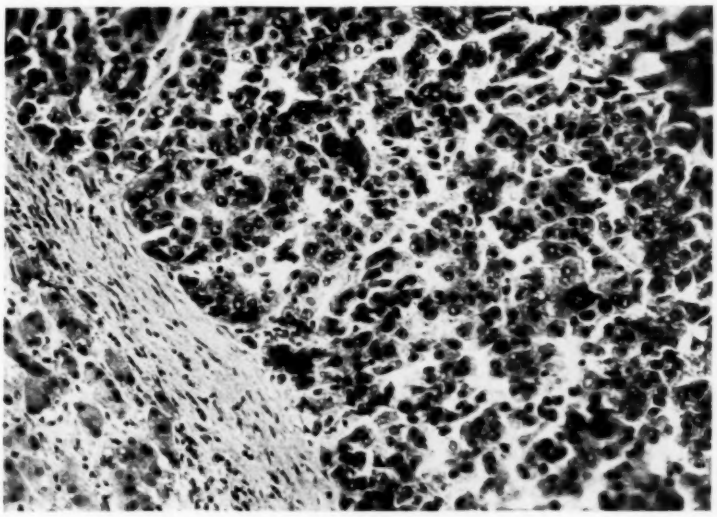

Fig. 4.—Photomicrograph of liver section through neoplastic growth, showing the character of malignant cells. (×240.)

ance. The gall bladder was small and contained 5 c.c. of pale, slightly turbid brown bile, but its walls were greatly thickened by edema.

The stomach and intestines were much distended by bloody fluid and some gas. The stomach contained 460 c.c. of thickly clotted blood and bloody mucus, together with a matted mass of hair, double fist size. The gastric wall was covered by very tenacious bloody mucus. The muscular and serosal coats appeared normal. In the small intestines were about 250 c.c. of blood and bloody mucus, which also extended down to the colon.

The microscopic section of the liver revealed a well-developed cirrhosis with pronounced liver cell regeneration, together with scattered fatty changes. The tumor was found to be a hepatic cell carcinoma subdivided into small nodules by bands of dense connective tissue (Fig. 3). The different areas varied greatly in appearance, ranging from benign-appearing hepatoma to highly malignant papillary or syncytial carcinoma. In general, the malignant cells grew in cords which were separated by sinusoids or by young connective tissue (Fig. 4). A tumor thrombus was seen in one large vein. The intrahepatic metastases were similar in type.

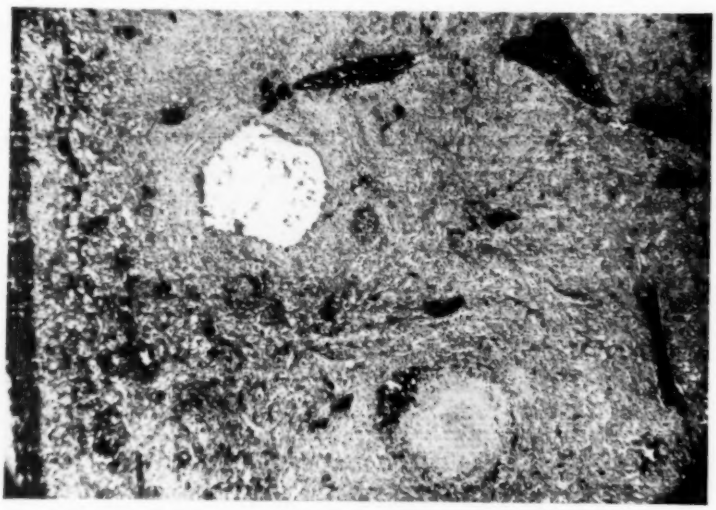

Fig. 5.—Photomicrograph of section of surgically removed spleen, showing small areas of fibrosis beneath the capsule, dilated blood vessels, and atypical Malpighian body. (Mallory's anilin blue-orange G stain, ×60.)

A section of the surgically removed spleen demonstrated a greatly thickened capsule, a reticular hyperplasia of the pulp, diffuse fibrosis with channelization and some thickening of fibrous trabeculae, with partial occlusion of some of the veins (Fig. 5). Small foci of hematopoiesis were present. The lymphoid tissue was relatively decreased. Several of the veins examined gave evidence of endophlebitis.

The marrow sections from the sternum and the rib dorsal and lumbar vertebrae were completely hyperplastic, with a large number of eosinophilic myelocytes.

COMMENT

The present case is unusual in that the primary carcinoma of the liver, although limited in its metastatic activity within the organ of origin, produced a train of symptoms which clinically suggested the

possibility of Banti's disease. Doubtless the liver pathology was primarily responsible for the production of extensive cirrhosis in this organ, which, by obstructing the portal circulation, caused the enlargement of the spleen. With splenomegaly the collateral circulation asserted itself, with the consequent distention of the esophageal and gastric veins as well as the appearance of caput medusae over the anterior walls of the chest and abdomen. The sluggish blood flow in the collateral channels led to the formation of tortuous varices on the mucous surfaces of the esophagus and the stomach. It was then only a matter of slight traumatization which caused the engorged veins to rupture and produced the alarming hemorrhages.

Hematologically this case consistently revealed a generalized depression in all the formed elements of the circulating blood, which can be explained on the basis of the above train of symptoms. The anemia was primarily due to extensive liver pathology as well as to hemorrhage and, secondarily, to the blood destruction taking place in the spleen. Leucopenia and thrombocytopenia likewise may be explained on the same basis. In the presence of thrombocytopenia no portal thrombosis could have occurred, since an elevation in blood platelet count is most likely to be associated with thrombosis of the portal system (Klemperer, 1928). The hyperplastic bone marrow was probably a result of stimulation occasioned by increased blood destruction and hemorrhage.

The question arises at this point as to the nature of the disease or the symptom complex bearing the name of Banti. Many cases of splenomegaly associated with cirrhosis of the liver, ascites, jaundice, and a hypoplastic blood picture have been reported under the name of Banti's disease. While this symptom complex constitutes an essential feature of the disease described by Banti, the underlying cause may be quite different in each case. The review of the literature dealing with reports of cases presenting this symptom complex reveals at least the following three distinct types of disease:

1. Banti's disease proper occurs chiefly in young adults and in older children, and is characterized by splenomegaly and liver cirrhosis, severe anemia, and leucopenia. Occasional hematemesis, subicteric bronzing of the skin, and ascites are also frequently seen, although these are relatively late in appearance. Pathologically, *fibroadenie* of the spleen, in addition to cirrhosis of the liver, is an essential feature of the disease.

2. The Smith-Howard-Wallgren syndrome is seen most frequently in infants and young children. The most conspicuous clinical manifestation, that which usually brings the patient to the attention of a physician, is copious hematemesis. The hemorrhage, due to the spontaneous and traumatic rupture of the esophageal and gastric varices, may recur at irregular intervals and usually is accompanied by changes in the size of the spleen, shrinking after hemorrhage and again enlarging after restoration of the normal blood volume. As Smith (1920) and

Wallgren (1927) pointed out, portal thrombosis in children may be secondary to infection. The blood picture is usually normal except for the development of posthemorrhagic anemia.

3. Neoplastic diseases of the liver, occurring at any age period, are also clinically characterized by progressive splenomegaly, early hepatomegaly with cirrhosis of varying degrees, ascites, icterus, establishment of collateral circulation due to portal obstruction, and a hypoplastic blood picture. Presumably the clinical manifestations and course depend primarily upon the extent and nature of the hepatic tumor. Petechial hemorrhages result from thrombocytopenia.

It is apparent from the above comparison of these three distinct diseases that the symptom complex in each is so identical that differentiation on physical and laboratory findings alone is often extremely difficult. Only autopsy can finally determine the correct diagnosis.

Pathologically, the most constant finding is the presence of cirrhotic changes in the portal areas of the liver, which may be quite extensive. In the neoplastic diseases of the liver, tumor nodules are quite easily demonstrated; some of them may be definitely encapsulated, but numerous metastases also may be found in various parts of the organ. Singularly, extrahepatic metastases are rare. If the tumor mass is situated near the gall bladder, the bile duct may be so compressed as to produce a marked bilirubinemia. The spleen usually shows a thickening of the capsule and trabeculae in degrees corresponding with the duration of the disease. In typical Banti's disease, the fibrous changes are so outstanding that Banti regarded *fibroadenie* to be quite essential as a diagnostic criterion. However, *fibroadenie* does not suggest any special type of pathology but merely represents an extreme degree of fibrosis of the organ. The pulp of the spleen usually reveals reticular cell hyperplasia, passive congestion, and hemosiderosis, with a concomitant reduction in the lymphoid tissue.

SUMMARY

A case of primary carcinoma of the liver is reported which occurred in a 6-year-old female child and was characterized by the pronounced cirrhotic changes in the organ, resulting in the development of collateral circulation (caput medusae), esophageal and gastric varices (hematemesis), splenomegaly, ascites, and a hypoplastic blood picture.

Analysis of the train of symptoms in this case suggests the advisability of regarding the symptom complex seen in neoplastic diseases of the liver, in Banti's disease proper, and in the Smith-Howard-Wallgren syndrome as indistinguishable from one another, even though each may differ in its fundamental etiology. Clinically, however, all these conditions are typified by their common manifestations resulting from similar sequences of events, all of which may be conveniently designated as "Banti's syndrome."

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THE INVOLVEMENT OF THE NERVOUS SYSTEM IN SICKLE-CELL ANEMIA

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SYMPTOMS and signs referable to the central nervous system have been noted frequently in patients with sickle-cell anemia. However, only recently has this type of involvement received special attention. The number of cases which have been observed, both clinically and at autopsy, is now large enough to warrant an attempt to clarify the picture of nervous system involvement.

It is the purpose of this paper to present six new cases of sickle-cell anemia with cerebral complications, to review the literature referable to central nervous system manifestations, and to contribute observations concerning the pathology.

CASE 1.—M. S., a negro boy, was first seen at the age of 20 months, at which time he was admitted with a history of progressively deepening unconsciousness for three days, associated with dyspnea. A similar attack had occurred one month previously. The child was comatose. Detailed neurologic findings were not recorded. The blood was typically that of sickle-cell anemia.

At the age of 3 the patient began having convulsions, which were followed by progressive paralysis of the left arm and leg.

Four months later, the child was admitted to the hospital after an illness of seven days, characterized by general aching which was more severe in the extremities, high fever, delirium, stiffness of the back, inability to stand, weakness of the left arm and leg, epigastric pain, and bloody urine. Anorexia and constipation were present, as well as pain in the rectum not related to defecation. The left eye was slightly swollen. At the onset, he had complained of sore throat and cough accompanied by retrosternal pain. The child was mentally normal. A spastic left hemiparesis was present, with increased patellar reflex and positive Babinski sign on the left, but no ankle clonus or Kernig sign. There was pain on flexion of the left knee. The right leg was normal. The neck was not stiff. There was evidence of mild upper respiratory tract infection.

Gradual improvement occurred, but he was unable to sit up for several weeks following discharge. He did not walk again for a period of one year, but crawled about on the floor. In addition, his arms were so weak that for several months he was unable to lift objects. When he finally began to walk again, his left knee was drawn up, and he walked on his left toes as he limped along. Gradually his gait improved, and he gained in weight and strength.

When the patient was 6 years old, he was readmitted with aphasia of five days' duration, accompanied by restlessness, a clouded mental state, and inability to stand. He had had an upper respiratory tract infection for one week. The child was semistuporous, moaned and groaned unintelligibly, tossed about in bed, and was very irritable. There was a left facial weakness. The neck was slightly stiff, and

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there was a positive Brudzinski sign. All the deep reflexes were hyperactive. The abdominal reflexes were present, but the cremasteric reflexes were absent. The pupils were normal; the sclerae were greenish-yellow. The nail beds were cyanotic.

Cerebrospinal fluid obtained by lumbar puncture in horizontal position on the day after admission was clear and under a pressure of 150 mm. of water. The Queckenstedt test was normal. The globulin test was negative. Only two cells per cubic millimeter were present. The Levinson and tryptophane tests were negative. The spinal fluid chlorides were 680 mg. per 100 c.c.

The patient remained in a semistupor and would not talk. He stared into space vacantly between half-opened lids and was at times markedly restless. A horizontal nystagmus when looking to the left developed.

The reflexes continued to be hyperactive. A transfusion of 200 c.c. citrated blood on the fifth hospital day had no apparent effect upon the condition.

On the eighth hospital day he developed clinical and roentgenologic evidence of pneumonia in the right lung.

The extremities were very spastic at this time, the left more so than the right, and the ankle clonus was stronger on the left than on the right. The Kernig and Babinski signs were strongly positive bilaterally, and the superficial reflexes were absent. A few hours before death on the fourteenth hospital day there was relaxation of all the previously spastic parts, and the deep reflexes became normal.

Autopsy was performed several hours after death by Dr. Gillespie.

Anatomic Diagnosis.—Sickle-cell anemia with sickled erythrocytes, retention jaundice, hemosiderosis, hyperplasia and congestion of the bone marrow, hepatomegaly, siderofibrotic atrophy of the spleen, osteoporosis of the inner table of

Fig. 1.—Sickle-cell anemia. Case 1. Osteoporosis of the inner table of the frontal and parietal bones.

skull, atrophy of the right cerebral cortex (probably due to thrombosis of the cortical branches of the right middle cerebral artery), dilation of the ventricles, particularly the right lateral ventricle, chronic adhesive leptomeningitis with pig-

Fig. 2.—Sickle-cell anemia. Case 1. Congestion of vessels over the hemispheres. Edema of the brain and atrophy of the right cerebral cortex.

Fig. 3.—Sickle-cell anemia. Case 1. Frontal section of the brain. Atrophy of right cerebral cortex. Dilation of ventricles, particularly the right lateral ventricle. Congestion of peripheral vessels. Edema and encephalomalacia.

ment deposits, acute congestive and hemorrhagic leptomeningitis, recent thrombus of the left middle cerebral artery, encephalomalacia; bronchial pneumonia; ulcer of the tongue; pulmonary tuberculosis, childhood type with peribronchial and mediastinal tuberculous adenitis, and bilateral pleural adhesions.

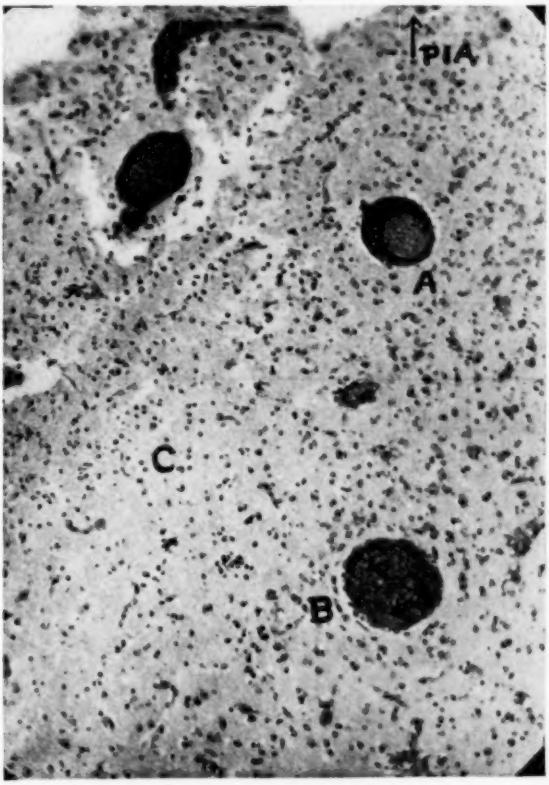

Fig. 4.—Sickle-cell anemia. Case 1. Left subpial cortex. *A*, Vessel congested with sickle cells; cellular infiltration in vessel wall; absence of perivascular infiltration. *B*, Early thrombosis with necrosis of vessel wall. *C*, Degenerative cortex.

The external surface of the skull revealed no abnormality. Multiple depressions, more marked on the right than on the left, were found on the inner surface of the frontal and parietal bones (Fig. 1). When the dura was incised, a large amount of dark brown fluid escaped. The dura was adherent to the arachnoid in the region of the right cerebral cortex. The dural sinuses were patent. The surface of the entire brain was congested, the most marked congestion being over the anterior and lateral surfaces of the hemispheres, and more marked over the left than the right (Fig. 2). The subarachnoid space in areas of greatest congestion was filled with a greenish-brown gelatinous fluid. The brain was edematous and very soft, and it could not be handled without tearing. The right cerebral cortex was smaller than the left. The atrophy involved the middle and inferior frontal gyri, the greater part of the anterior and posterior central gyri, the inferior parietal lobule, and the superior and middle temporal gyri. At the base of

the brain and around the upper portion of the spinal cord there was moderate congestion, thickening of the meninges, and slight brownish pigmentation.

The arteries of the circle of Willis were dilated but contained no clots. Adherent dark red clots were present in the superficial branches of the left middle cerebral artery. The cortical branches of the right middle cerebral artery were small and could not be traced in the thickened meninges.

Multiple sections through the brain revealed gross atrophy of the white and gray matter of the right cortex. The ventricles and particularly the right lateral ventricle were dilated. There were no gross lesions in the cerebellum or basal ganglia (Fig. 3). The vessels of the choroid plexus were filled with blood. The pituitary and pineal glands were normal.

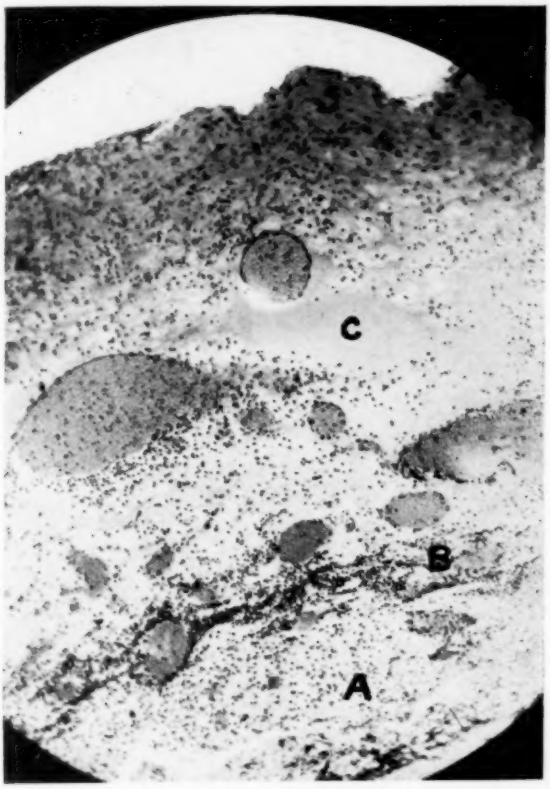

Fig. 5.—Sickle-cell anemia. Case 1. *A*, Cerebral cortex; neuroglial proliferation; capillary stasis. *B*, Thickened pia; dilated vessels; inflammatory exudate. *C*, subarachnoid space containing serofibrinous and cellular exudate. Congested vessels and hemorrhage.

Multiple sections taken from different portions of the left cortex revealed diffuse degenerative changes, with practical disappearance of well-preserved neuronal elements and an increase of glia cells and inflammatory cells. In the subpial region there were areas of frank necrosis. Throughout the gray matter of the left hemisphere dilated blood vessels were conspicuous. In some of these vessels there were accumulations of white cells within the lumen and degenerative changes in

the vessel wall; in others there was cellular infiltration within the walls (Fig. 4). Perivascular edema, cellular infiltration, and hemorrhage were demonstrable. Partial and complete thrombosis and necrosis of thrombosed vessels were observed. There

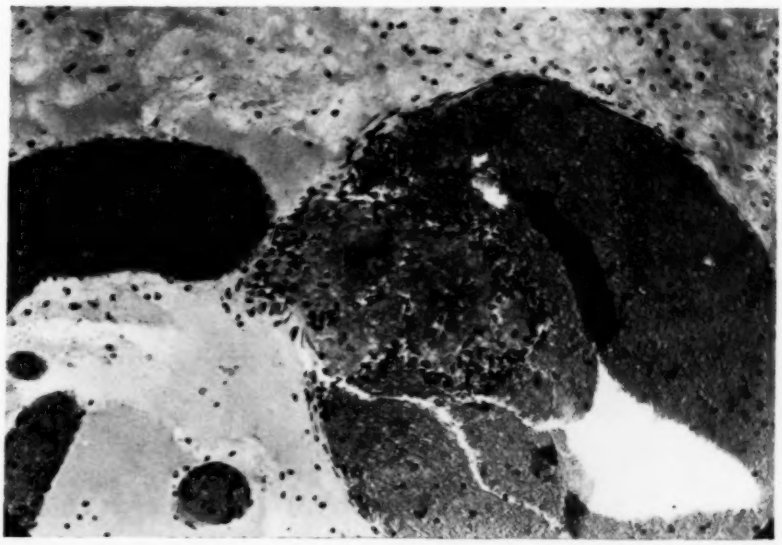

Fig. 6.—Sickle-cell anemia. Case 1. Beginning thrombosis of dilated vessel in subarachnoid space. Serofibrinous exudate.

Fig. 7.—Sickle-cell anemia. Case 1. Arteriole in subarachnoid space. Polypoid-like proliferation of intima into lumen. Congestion with sickled cells. Serofibrinous and cellular exudate.

were numerous recently thrombosed capillaries containing degenerated cells and appearing as bluish and granular, branching strands with poorly preserved endothelial boundaries.

The pia and arachnoid were thickened and infiltrated with inflammatory cells. The subarachnoid space was in places obliterated by organized fibrous tissue, but in other places it was distended with serofibrinous exudate. The blood vessels were filled with sickled cells, and there was diapedesis of erythrocytes and cellular exudation (Fig. 5). Many of the congested vessels contained fresh thrombi (Fig. 6). In some of the arterioles within the subarachnoid space there was peculiar polypoid-like proliferation of the endothelium within the lumen of the vessels (Fig. 7).

A section through the left middle cerebral artery revealed a red cell thrombus in which there was beginning organization. The internal elastic lamella, media, and adventitia of this vessel were normal, and there was no intimal proliferation.

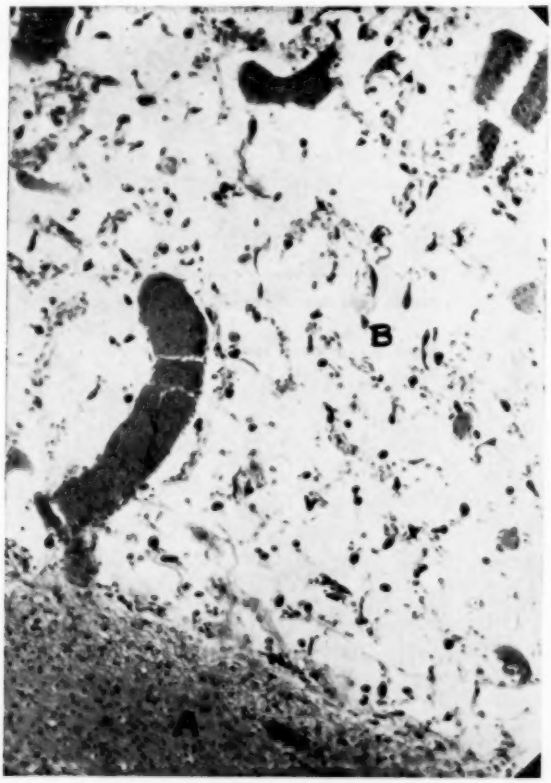

Fig. 8.—Sickle-cell anemia. Case 1. Surface of right hemisphere. *A*, Atrophic cortex. *B*, Subarachnoid space. Fibroblastic proliferation. Phagocytosed blood pigment.

Sections through the right cerebral cortex revealed the same types of vascular lesions as in the left. The subarachnoid space was practically obliterated by organized fibrous tissue. The arachnoid was thickened; its surface was irregular and more vascular than normal. Round and stellate cells containing brown and black pigment granules were conspicuous in some areas (Fig. 8). In some areas the sub-

pial cortex was replaced by small cystic areas. There was marked proliferation of neuroglial structures and a practical absence of ganglion cells.

Sections through the cerebral peduncles revealed atrophy of the substantia nigra and some atrophy, distortion, and degeneration of the fibers of the base of the peduncle on this side. Sections through the upper portion of the cervical spinal cord revealed partial adhesive arachnoiditis with pigment deposits. The blood vessels were dilated. Hyalinized thrombi were demonstrable in a few of the smaller vessels.

Discussion.—The osteoporosis of the skull occurs at points most distant from the larger arteries of the skull and probably represents decalcification associated with increased blood flow through anastomotic channels between the skull and the dura. The area of atrophy in the right cortex corresponds with the distribution of the superficial branches of the middle cerebral artery. Previous thrombosis of these branches is assumed. The dilation of the ventricles is in part compensatory and due to atrophy of the brain substance, but in part due to interference with fluid absorption caused by obliteration of the subarachnoid spaces over the hemispheres.

CASE 2.—C. S., a negro male, gave a characteristic history of sickle-cell anemia. The diagnosis was confirmed by physical examination, the blood picture, and other laboratory findings on two hospital admissions. At the age of 6 the patient had a "stroke." The patient did not remember the details, but he had had a severe headache and fever and had been unconscious for a while. Following this sickness he was unable to use his right hand and arm, but gradually regained partial motor function. The right leg was stiff, and the right foot dragged when he walked. He was unable to do any kind of manual labor. The right arm and leg and the right side of the thorax were smaller than the similar parts on the left. The reflexes of the right extremities were hyperactive.

Death occurred at the age of 26 years, with terminal nephritis and uremia.

The autopsy was performed on the unembalmed body several days after death by Dr. Diggs.

Anatomic Diagnosis.—Sickle-cell anemia, emaciation, maldevelopment, sickle erythrocytes, congestion of capillaries, jaundice (retention type), hemosiderosis of reticuloendothelial system and kidney, atrophy of the left cerebral cortex, pigmentary remains of old meningeal and subpial hemorrhage, multiple subpial cysts, chronic adhesive arachnoiditis, pachymeningitis. Atrophy of muscles of the right trunk, particularly of the right arm. Cardiac hypertrophy, fibrinous pericarditis with effusion, atherosclerosis of the aorta. Siderofibrosis and atrophy of the spleen. Hepatomegaly, parenchymatous degeneration, proliferation of Kupffer cells, chronic cholecystitis, and cholelithiasis. Fibrosis and atrophy of the left adrenal. Hyperplasia of bone marrow; osteoporosis of skull, flat bones of trunk and ends of long bones, distortion of trabecular pattern, interosseous new bone formation in shafts of long bones. Chronic leg ulcers. Chronic diffuse glomerulonephritis and nephrosclerosis, multiple cysts of kidney, generalized edema. Chronic pleuritis, bilateral. Dental caries, pyorrhea.

The left cerebral hemisphere was smaller than the right, and in the anterior and lateral portion there was a yellowish-brown area of atrophy and scarring, measuring 9 by 5 cm. Over this area the dura was attached and the meninges were thickened and adherent. The meningeal blood vessels around this area were dilated. The

center of the area was in the posterior portion of the middle frontal gyrus. The areas involved included the middle frontal gyrus, the medial portion of the anterior central gyrus, and small portions of the posterior central gyrus and superior frontal gyrus. The area involved corresponded to the distribution of the anterior superficial branches of the middle cerebral artery (Fig. 9).

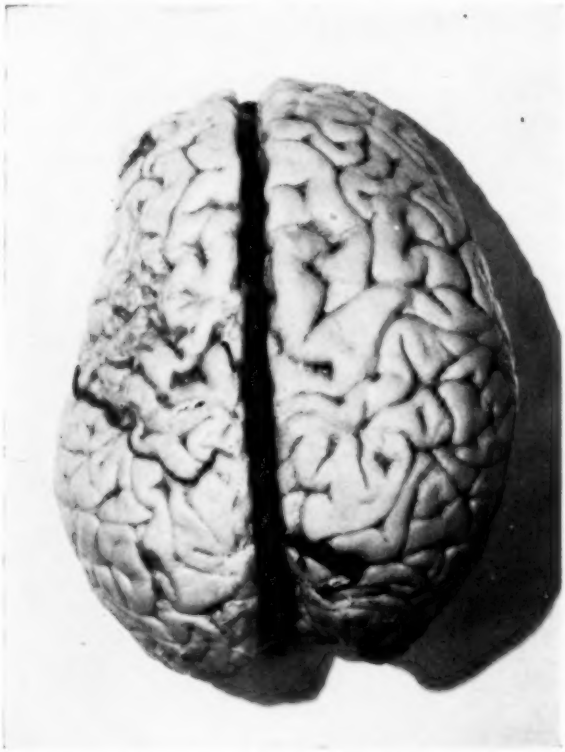

Fig. 9.—Sickle-cell anemia. Case 2. Atrophy of the left cerebral cortex.

On section the atrophy was seen to involve the gray and white matter of the cerebral cortex and did not involve the deeper structures. The left ventricle was dilated. The temporal and occipital lobes, cerebellum, and medulla were not involved (Fig. 10). The vessels at the base of the brain and the lateral and central sinuses were normal. Dissection of the proximal portion of the middle cerebral artery failed to reveal any thrombus, but the arteries leading to the involved area were much smaller than those on the unaffected side and it was impossible to follow them into the atrophic area.

The microscopic examination of the atrophic gray and white matter of the left cerebral cortex revealed a decrease in pyramidal cells and an increase in neuroglial elements. In some fields there were no nerve cells demonstrable. Small cystic areas were present in the subpial region. The capillaries in the scarred cortical area were distended with sickled erythrocytes. The smaller arterioles revealed endothelial proliferation and hyalinization. The pia was thickened and contained yellow and brown pigment granules, free and in the cytoplasm of the connective

tissue phagocytes. Some of these granules gave a positive reaction for iron. Astrocytes and cells with round nuclei and inconspicuous cytoplasm were numerous in the peripheral layers of the cortex.

Fig. 10.—Sickle-cell anemia. Case 2. Sagittal section through the left hemisphere. Atrophy of cortex and dilation of ventricle.

The subarachnoid space was completely obliterated by fibrous tissue in places and partially obliterated in others. The meninges were thickened. The meningeal vessels were numerous. For the most part they were empty and appeared normal in structure, but there were occasional arterioles which showed hyperplasia of endothelium, splitting and distortion of elastica, and narrowing of the lumen.

Sections through other parts of the brain revealed no abnormalities in blood vessels or brain structure.

The meninges of the spinal cord were moderately thickened and were infiltrated with round cells.

CASE 3.—A. M. C., a 15-year-old negro girl with typical sickle-cell anemia, frequently complained of frontal headache and a tired aching feeling of the eyes. On one occasion she suddenly became blind. No cause for her blindness could be found. Three days later her vision returned partially, and on the fourth day she was able to see well. Frontal headaches and aching of the eyes continued intermittently. Later, the patient, then 18 years old, began to have abdominal discomfort, headache, nausea, restlessness, and fever. On the third day of illness she began to talk

irrationally and lapsed quietly into a state of coma. There were no convulsions or delirium. Examination showed the patient to be limp and unresponsive. The neck was not stiff. The remainder of the examination was negative except that no reflexes could be obtained other than the reaction of the pupils to light. In one week the patient improved sufficiently to walk about.

CASE 4.—L. C., a 10-year-old negro boy with sickle-cell anemia, was admitted to the hospital because of pain and stiffness of the back of two days' duration. The neck was stiff, and the Brudzinski and Kernig signs were positive. Lumbar puncture showed only 7 cells per cubic millimeter, and they were all lymphocytes.

The back and legs remained stiff for three days, and then the rigidity gradually disappeared over a period of several days. At times the patient complained of spots before the eyes, diplopia, and photophobia. Subsequent examinations revealed no residual neurologic symptoms or signs.

CASE 5.—A. F., a 4-year-old negro girl with sickle-cell anemia, was admitted to the hospital because of marked drowsiness of one week's duration, associated with abdominal pain, vomiting, marked anorexia, yellowish discoloration of the eyes, and the excretion of dark brown urine. Similar attacks had occurred every two or three weeks for one year. The patient was stuporous and was irritable when aroused. She resisted examination. The neck was slightly stiff, but there were no other neurologic abnormalities.

Spinal puncture revealed clear fluid under normal pressure. The Queckenstedt test was normal. The Ross-Jones test for protein was positive. There were 6 cells per cubic millimeter. The Levinson and tryptophane tests were negative. The spinal fluid sugar was 84 mg. per 100 c.c.

She gradually became less apathetic and within a week's time had returned to her normal condition.

CASE 6.—B. M. P., a 5-year-old negro girl with typical sickle-cell anemia, developed abdominal pain and spasticity associated with a respiratory infection. There was occasional vomiting. Within a few days the neck and back became rigid, the legs became spastic and could not be straightened, and there was generalized hyperesthesia, more marked in the lower extremities. The patient was admitted with a tentative diagnosis of meningitis; however, the cerebrospinal fluid was clear and colorless, the pressure was not increased, no white blood cells were seen in the cubic millimeter examined, the globulin was negative, and the sugar was 67 mg. per 100 c.c. Physical signs and roentgenograms revealed pneumonia in the right lower lobe. Following the administration of sulfanilamide, the general condition improved, and the spasticity and hyperesthesia decreased. Residual tenderness and resistance to movement of the right hip persisted for about a week, but this likewise cleared up.

Other Observations.—In a series of fifty-five patients with sickle-cell anemia who have been followed at frequent intervals during the last eleven years at the John Gaston Hospital, headaches have been a frequent and bothersome symptom. Epistaxis is also a frequent symptom, although hemorrhages from other mucous surfaces are rare and purpuric skin manifestations have not been observed. Often the epistaxis is followed by relief of headache. Drowsiness, dizziness, minor visual and auditory disturbances, and fainting are common. Occasionally there is localized facial swelling and dilation of superficial facial vessels unaccounted for by inflammatory lesions.

Attacks of severe pain anywhere in the body, from the top of the head to the soles of the feet, are part of the clinical picture during the acute febrile attacks. The pains are most often in the joints, but severe abdominal and chest pains resembling tabetic crises and acute surgical conditions are also seen. Sometimes the pain is referred to bones or muscles. Low back pain is common. Pains usually begin fairly suddenly and remain constant for hours and sometimes days, gradually subsiding. Usually there is no residual lack of function of the part involved. Priapism has been observed in two patients.

REVIEW OF PREVIOUSLY REPORTED CASES

CASE 1.—Sydenstricker, Mulherin, and Houseal[1] were the first to record nervous system manifestations in sickle-cell anemia. They reported the case of a 5-year-old negro boy with left spastic hemiplegia, generalized rigidity, mental dullness, and frequently recurring, painful, tonic convulsions. When not in tonic spasms the patient lay quietly in bed, but was apparently in considerable pain. The deep reflexes were hyperactive, especially on the left. The spinal fluid was normal. Death occurred during a convulsion on the eighth day.

CASE 2.—Graham[2] reported the case of a 30-year-old negro man with severe pain in the occipital region, neck, and back, associated with retraction of the head and stiffness of the neck. Similar attacks had occurred previously. The spinal fluid was grossly bloody on the second day. The patient contracted a respiratory infection and died. At necropsy the brain tissue, the meninges, the spinal cord, and the cerebrospinal fluid were yellow. No other changes were noted. The vessels of the brain were reported as normal.

CASE 3.—Hamilton[3] reported the case of a 21-year-old negro soldier who had recurrent attacks of sleepiness and drowsiness associated with pains in the back, abdomen, and extremities. The patient "fell out" on the drill field with severe occipital, back, heart and extremity pains. There were flexion of the extremities and retraction of the neck. A lumbar puncture relieved his pain immediately. No report of the nature of the fluid was made. Subsequently, he had several similar, but milder, attacks.

CASE 4.—Bell, Kotte, and Mitchell[4] reported the case of an 18-month-old negro boy with frontal headache, pain in the lumbar region, stiffness of the neck, and refusal to walk.

CASE 5.—Cook[5] reported the case of a negro boy who at the age of 4 had had "spinal meningitis" which left him a cripple. At the age of 7 there were sudden unconsciousness, coma, hyperpnea, and left flaccid paralysis. All the deep reflexes were absent. The pupils were irregular and fixed; there was bilateral nystagmus, and two fresh hemorrhages were seen in the right fundus. Lumbar puncture revealed yellowish fluid under increased pressure. The globulin was markedly increased. There were 130 white blood cells and 1,400 red blood cells per cubic millimeter, the red cells being sickled. The patient died three hours after admission. Necropsy revealed subarachnoid hemorrhage with cerebral softening on the right. No microscopic findings were recorded.

CASE 6.—Leivy and Schnabel[6] recorded the case of a 4-year-old negro girl who had had attacks of convulsions and coma for the previous two years, as well as symptoms typical of sickle-cell anemia. The skull roentgenogram showed "evidence of cerebral atrophy due to intracranial pressure." The patient returned repeatedly with similar attacks. Detailed neurologic findings were not reported, nor was a spinal puncture mentioned.

CASES 7 and 8.—Anderson and Ware[7] reported the case of a 10-year-old negro girl admitted in an unconscious state, just after a convulsion. No neurologic findings were reported, nor was a spinal puncture mentioned. The patient died two days after admission. Autopsy revealed bronchopneumonia, massive focal necrosis of the lungs, and changes typical of sickle-cell anemia. No mention was made of the nervous system findings.

The same authors reported the case of a 9-year-old negro girl with sickle-cell anemia who had a hemiplegia "of undetermined origin." Improvement occurred in three weeks.

CASE 9.—Corrigan and Schiller[8] observed a 7-year-old negro boy who had convulsions, fever, and irritability. The neck was slightly stiff. The patient showed gradual improvement.

CASES 10, 11, 12, 13, and 14.—Arena[9 and 10] reported five cases of sickle-cell anemia with neurologic findings.

CASE 10.—A 6-year-old negro boy had headache, impairment of speech, dizziness, drowsiness, and unconsciousness for one day before admission. The left arm and leg made spasmodic movements. The right limbs were powerless. A brother had died recently with symptoms similar to those of the patient. The child was in a semistupor. The deep reflexes were hyperactive, and the Babinski sign was present on both sides. Bloody spinal fluid was obtained on three occasions. The patient remained in a semistupor, and the right arm and leg became spastic. The patient gradually improved, but residual spastic right hemiplegia and right facial weakness ensued.

CASE 11.—A 6-year-old negro boy had paralysis of the right side of two days' duration. He had had attacks of petit mal since the age of 2 years. The right arm and leg were weak; there was right facial weakness, deviation of the tongue to the right, hyperactive deep reflexes, and a positive Babinski reflex on the right. Residual spastic right hemiplegia and right facial weakness persisted.

CASE 12.—A 10-year-old negro boy had had spastic right hemiplegia suddenly at the age of 6 years. He had definite nystagmus in all directions. The deep reflexes on the right were hyperactive, and the Babinski reflex was positive on the right. He had sustained ankle clonus on the right.

CASE 13.—A 4-year-old negro boy had paralysis of the right side of three weeks' duration, which had followed closely a sudden headache and an episode of vomiting. He had difficulty in swallowing, chewing, and talking. There was almost complete spastic paralysis on the right and right facial weakness. The deep reflexes on the right were hyperactive and accompanied by a positive Babinski reflex. No improvement occurred.

CASE 14.—A 4-year-old negro girl suddenly developed aphasia. Two weeks later right hemiplegia occurred. Three other siblings, one a known case of sickle-cell anemia, had died with a similar condition. The patient could neither walk nor speak, but could comprehend commands and questions. The tongue could not be moved. Paralysis, weakness, and spasticity of the right arm and leg were present. Reflexes were hyperactive throughout, but more marked on the right side. The spinal fluid was normal. Partial improvement occurred during the next three and one-half years. Then the child had a sudden attack of pain in the left frontal region and crumpled to the floor. Both her legs were paralyzed, and she was unable to speak. She became unconscious and had a right spastic hemiplegia. The left arm was also spastic, but the left leg was limp. Tendon reflexes were hyperactive on both sides, more so on the right. Kernig and Babinski signs were positive bilaterally. The spinal fluid showed an initial pressure of 270 mm. The fluid was bloody, showed slight xanthochromia, and contained 30,000 red blood cells per cubic millimeter. She died fifteen hours later.

The pathologic findings in this case were reported by Bridgers.[10] He observed and gave excellent illustrations showing widespread congestion, hemorrhages involving the meninges and the gray matter, encephalomalacia, atrophic changes in the cortex and pyramidal tracts, and dilation of the ventricles. The lumina of the right middle cerebral artery and the left ascending branch of the left middle cerebral artery were completely obliterated, and other vessels showed partial obliteration. Endothelial proliferation, fibroblastic reaction, hyalinization, fragmentation and partial loss of internal elastic lamina, inflammation and necrosis of vessel walls, perivascular hemorrhages, and iron deposits were noted in various arteries. No proliferation of endothelium was noted in the minute vessels of the brain substance, but capillary engorgement with sickled erythrocytes was a prominent feature.

CASE 15.—Penberthy and Cooley[10] observed a boy with sickle-cell anemia who had recurrent epileptiform attacks.

CASE 16.—Ryerson and Terplan[11] reported a case of a 3-year-old negro girl who was admitted in a semicomatose condition, became rapidly comatose, and died shortly. The pathologic findings were typical of sickle-cell anemia. No mention was made of the changes in brain or cord.

CASE 17.—Baird[12] reported the case of a 42-year-old negro male who experienced a cerebral accident characterized by deep coma from which he gradually emerged. However, aphasia, nasal regurgitation, and marked salivation persisted, and the patient was completely disoriented and constantly gibbering. One year previously he had had an attack of total blindness which lasted two weeks. Ten weeks after the cerebral accident, he died with symptoms of cardiac decompensation. The brain was not examined.

CASE 18.—Yater and Hansmann[13] described the pathologic findings in a 38-year-old negro woman with sickle-cell anemia who had multiple thrombi in the smaller arteries of the lung, cor pulmonale, and cardiac failure. Paresthesias of the extremities and "wild excitement" previous to death were the only nervous system symptoms recorded. Examination of the brain, however, showed congested superficial vessels, diapedesis of blood, pigment deposits and large mononuclear cell reaction in the meninges and superficial layers of the cortex, and sclerosis of the choroid plexus. Small hemorrhages were present in the spinal meninges, and there were patchy areas of fibrosis. Focal areas of hemorrhage and nerve cell degeneration were present in the spinal cord. An abnormal number of corpora amylacea were present in the cord, particularly in the posterior columns. The vessels of the nerve trunks were packed with sickled cells.

CASE 19.—Kampmeier[14] observed the case of a 13-year-old negro boy who had been repeatedly hospitalized because of stupor, convulsions, and colicky abdominal pain. After five of these episodes in an interval of three years, there resulted residual spasticity on the right side. The spinal fluid findings were normal except upon the last admission when frankly bloody fluid under increased pressure was observed. The fluid became xanthochromic, and the pressure returned to normal within a few days. On the last admission the patient was comatose. The pupils reacted sluggishly to light. There was paralysis of the right side of the face and ptosis of the right eyelid. Spastic right hemiplegia was present. The tendon reflexes were markedly hyperactive, and right hemiplegia was present. A positive Babinski reflex was present on the right; a Kernig reaction was apparent bilaterally. Ankle clonus was present on the right.

CASE 20.—De Azevedo[15] reported the case of a 12-year-old negro who became disoriented, was drowsy and apathetic, began to stagger, and developed aphasia. Inability to move the arms and legs and generalized spasticity occurred. Jacksonian convulsions ensued, involving particularly the right arm and right side of the face; at times the lower extremities and the left arm participated in the convulsions. The

eyes were fixed in a stare. All the deep reflexes were increased. Ankle clonus was present in both lower extremities. The spastic arms and legs were held in positions of flexion, and straightening the extremities produced cries of pain. Carphologia, occasional gnashing of teeth, and pica were present. The spinal fluid showed increased globulin. Albumin was 0.63 per cent.

At post-mortem examination the dura was found to be more adherent than normal. The leptomeninges were thickened. The blood vessels on the surface of both hemispheres were of increased caliber, and in some of these vessels there were recent thrombi. There were occasional hemorrhagic foci in the leptomeninges, but the cerebrospinal fluid was not grossly bloody. The lateral and longitudinal venous sinuses were dilated and contained grayish-red thrombi. The choroid plexus was hyperemic. Sections through the brain revealed enlargement of the lateral ventricles but no other gross changes. The brain stem was normal.

CASES 21 and 22.—Bosselman and Kraines[16] observed a 13-year-old negro boy who developed aphasia. He began to omit words when reading and did not understand corrections. Mispronunciation of words and lack of interest in his former routines became apparent. He spoke in a loud voice, did not respond when addressed, and on occasions seemed not to recognize members of his family. Restlessness was noted. Spoken and written replies to spoken questions and directions were inaccurate, but his responses to written questions and directions were perfect. Partial improvement in his aphasia took place, but he showed persistent changes in personality, particularly increased irritability and restlessness, a preference for infantile games, and a tendency to make grandiose statements.

Bosselman and Kraines also mention autopsy findings in a patient with sickle-cell anemia in whom there was chronic leptomeningitis and occasional recent extravasations of blood in the basal ganglia.

CASE 23.—Ford[17] reported an 18-month-old negro boy who suddenly began to vomit and became stuporous. The fontanels were tense and the optic disks showed edema. The legs were spastic with increased tendon reflexes, bilateral ankle clonus, and extensor response. The spinal fluid was bloody and under increased pressure. Blood could not be obtained from the longitudinal sinus. The stupor deepened, and the child died in convulsions. Post-mortem examination revealed a premortem thrombus in the superior longitudinal sinus, with softening and hemorrhagic infiltration of the superior frontal and parietal lobes of the hemispheres, extending almost to the fissure of Sylvius. There was also hemorrhage into the subarachnoid spaces over the superior and lateral surfaces of the brain which spread to some extent to the basal cisterna. The brain was swollen.

Ford mentions the finding of similar lesions in other cases of sickle-cell anemia.

CASE 24.—Josey [20] recorded the case of a 4-year-old negro boy who began to have at several months' intervals attacks of difficulty in talking, swallowing, and walking. He seemed normal between attacks. Between the ages of 6 and 8, spastic paralysis of the right side occurred. During the last attack there was generalized spasticity with hyperactivity of all the tendon reflexes. The child was in a peculiar mental state of unresponsiveness, emitting stridulous cries. Sensation to painful stimuli seemed normal. The spinal fluid was normal. Gradual partial improvement occurred.

CASE 25.—Skoog[21] has reported the only case in which multiple cranial nerve palsies have occurred in addition to other neurologic phenomena. His patient, a 34-year-old negro male, suddenly became paralyzed on the right side and rapidly developed motor aphasia. One and one-half years after the onset of symptoms, right spastic hemiplegia and motor aphasia persisted, and, in addition, multiple cranial nerve involvement was noted. There was a complete paralysis of the third and fourth cranial nerves on the left. The left pupil was dilated. A complete ptosis of the left upper eyelid existed. Left homonymous hemianopia was noted. The eye grounds were normal. There was mild sensory impairment over the area supplied by the right fifth cranial nerve. The tongue deviated to the left when protruded, signifying involvement of the left twelfth cranial nerve. The entire right side of the body showed moderate anesthesia and analgesia. The mentality of the patient showed no impairment, but his responses were limited by the motor aphasia.

Cases of possible cerebral manifestations of sickle-cell anemia have been reported by Wollstein and Kriedel[22] and Hargrove and Mathews,[23] but these cases are not included in the series because the cerebral manifestations were not clearly related to sickle-cell anemia.

Harden[24] noted greatly dilated and tortuous arteries and veins in the eye grounds and tortuous and thickened superficial temporal vessels in a 9-year-old negro boy with sickle-cell anemia who had thickening of the skull with striking perpendicular trabecular markings. A younger brother had similar changes.

Bridgers[25] reported multiple petechial hemorrhages in the brain, lungs, and heart, and hemorrhagic infarction of the spleen in a 62-year-old negro woman whom he considered to have sickle-cell anemia. This case is not accepted as one of sickle-cell anemia, for the clinical, laboratory, and pathologic findings do not substantiate this diagnosis.

DISCUSSION

An accurate analysis of the clinical and pathologic findings in patients with sickle-cell anemia with central nervous system involvement is impossible, for the number of cases observed are relatively few, complete examinations are seldom made, the period of observation is short, and the reports are often lacking in essential details. The relative incidence of clinical findings as reported in twenty-five cases from the literature

and in six of our cases is given in Table I. It is apparent from the clinical records that neurologic manifestations are frequent in sickle-cell anemia patients, that the lesions are multiple, that the location of the lesions is variable, that the onset of symptoms is often sudden and is extensive enough to cause grave manifestations such as convulsions, meningeal signs, pains, aphasia, paralyses, coma, and death. The prognosis following central nervous system lesions is poor, but it varies widely and is unpredictable. Some patients may live for years after a major vascular accident and others die shortly after the first attack. In frequent patients there are recurrent episodes in which there are symptoms and signs referable to the nervous system. In these cases there is a tendency for the later attacks to be more severe.

TABLE I

SICKLE-CELL ANEMIA WITH CEREBRAL COMPLICATIONS: RELATIVE FREQUENCY OF NERVOUS SYSTEM SYMPTOMS IN THIRTY-ONE CASES

	NO. OF CASES
Drowsiness, stupor, or coma	16
Hemiplegia	14
Aphasia	9
Headache	8
Convulsions	8
Stiffness of the neck	8
Pain in the back and neck	7
Abdominal pain	7
Irritability	6
Facial weakness	5
Aching extremities	5
Stiffness of the legs	5
Stiffness of the back	4
Nystagmus	3
Pupillary changes	3
Vomiting	3
Transitory blindness	2
Ptosis	2
Generalized rigidity	2
Dysphagia	2
Paresthesia of extremities	2
Diplopia	1
Left homonymous hemianopsia	1
Paralysis of left 3rd and 4th cranial nerves	1
Weakness of left side of tongue	1
Anesthesia and analgesia of right side of body	1
Nasal regurgitation	1
Marked salivation	1
Delirium	1

The cerebrospinal fluid findings in nine cases from the literature and in three of our cases are summarized in Table II. It is to be noted that the cerebrospinal fluid findings are variable and often normal, although the patient has definite neurologic signs. It is also noted that fluids which on first examination were normal may later become abnormal. When abnormalities are found in the cerebrospinal fluid, they consist of increased pressure, sickled erythrocytes, xanthochromia, and protein and white cell increase.

TABLE II

SPINAL FLUID FINDINGS IN SICKLE-CELL ANEMIA WITH NERVOUS SYSTEM INVOLVEMENT

AUTHOR	COLOR OF FLUID	PRESSURE	PROTEIN	WHITE BLOOD CELLS	RED BLOOD CELLS	REMARKS
Sydenstricker	Clear					"Normal"
Graham	Bloody					
Cook	Yellow	Increased	Increased	130	1,400	Sickled Red Blood Cells
Kampmeier	Clear; Bloody	Increased				
Ford	Bloody	Increased				
Arena	Bloody				30,000	
	Clear; Bloody	270 mm. H_2O				
Josey	Clear					"Normal"
De Azevedo	Clear		Increased			
Authors' cases	Clear	Normal	Normal	2		
	Clear	Normal	Increased	6		
	Clear	Normal	Normal	0		

The lesions in the brains of patients with sickle-cell anemia who have cerebral complications are varied and widespread, but present features which are sufficiently constant to warrant certain generalizations. From the combined pathologic and clinical evidence and from analogy with the known pathologic processes in sickle-cell anemia in other organs, it is our opinion that the central nervous system lesions in sickle-cell anemia are primarily intravascular. The most common and constant cerebral changes found at autopsy are dilation of peripheral blood vessels and congestion with sickled erythrocytes. The congestion is most marked in the vessels in the cortical gray matter and in the vessels within the subarachnoid spaces over the hemispheres. Multiple thrombosis of smaller blood vessels in the same area is the rule. Sometimes there is thrombosis of the larger dural sinuses and cortical branches of the cerebral artery and, particularly, of the middle cerebral artery. Other vascular lesions in the small vessels include infiltrative and degenerative changes in the vessel walls, perivascular edema, cellular exudation, hemorrhage, and necrosis. In the larger arteries and arterioles which supply blood to the cerebral cortex there are alterations in the walls which include intimal proliferation, fragmentation and reduplication of intima, medial fibrosis and hyalinization, and sometimes hemorrhage into the media, with pigmentary changes and calcification. In these vessels the lumen is narrowed, and fresh and organized thrombi are found. The cortical and convolutional gray matter and, to a less extent, the white matter adjacent to it are involved in acute and chronic degenerative changes of various types. In the older and more extensive lesions there is gross atrophy and a practical absence of pyramidal cells and connective tissue proliferation. The central white matter, the basal ganglia, and the mid- and hindbrain are less likely to be involved than

the gray matter and periphery of the brain. These areas, however, are not entirely spared as is obvious from the clinical reports. The spinal cord has been studied inadequately, but the meager evidence that is available reveals meningeal and vascular lesions and degenerative changes in ganglion cells comparable to those found in the cerebral cortex. It is predicted that future studies will reveal gross spinal cord lesions in some cases. The tissue changes found in the brain are similar to those observed in the spleen and bone marrow in sickle-cell anemia in which there are stasis, thrombosis, infarction, parenchymal degeneration, and fibrotic atrophy.

The rate of blood flow through the numerous small vascular channels of the cortex is normally slow. Factors which increase the stasis are the presence of elongated and multipointed sickled erythrocytes, the increased number of leucocytes, nucleated red blood cells, macrocytes and platelets, and, in some cases, venous back pressure due to obliterative changes in the arterioles of the lung and to myocardial failure. Factors which favor anoxemia are the stasis of blood, the anemia itself, and the increased utilization of oxygen by the increased number of nucleated cells which are characteristic of the sickle-cell type of anemia. In the presence of anoxemia the sickling process is exaggerated, and there is vasodilation. Vasodilation and sickle-cell distortion in turn increase the anoxemia. The combination of stasis and anoxemia leads to endothelial injury and initiates clot formation. The large number of platelets which are present in the blood favor intravascular coagulation by forming platelet thrombi and by liberating thromboplastic substance.

Following thrombus formation in the given vessel, the blood flow is shunted through collateral channels which become still more dilated. The walls and perivascular tissues of these collaterals in which there is also stasis and anoxemia undergo infiltrative and degenerative changes. These vessels may in turn become thrombosed or may rupture, giving rise to hemorrhagic and pigmentary lesions in the meninges and cortex. The thrombi may extend to the larger veins or lead to thrombosis of arterioles and finally of major arteries.

Bridgers[18] is of the opinion that the endothelial proliferative and obliterative changes observed in the arteries in sickle-cell anemia are primary lesions and that the other phenomena are secondary. We confirm his findings in our material, but interpret the arterial changes as being secondary to capillary and venous thrombosis. The lesions observed are explainable on the basis of chronic stasis and a diminishing volume of blood flow as the parenchymal tissue becomes replaced by scar tissue.

The pathologic findings correlate well with the clinical manifestations. The milder symptoms, such as headache, drowsiness, dizziness, minor meningeal irritations, and temporary sensory and motor symptoms and signs, are probably explainable on the basis of vascular stasis and small

thrombi with good collateral circulation. In such lesions the cerebrospinal fluid would be normal, for there would be no hemorrhage, little perivascular involvement, no space-occupying mass or significant disturbance in the balance between fluid formation and absorption. In the more extensive lesions in which the thrombi involve larger vessels or multiple small vessels in areas in which the collateral circulation is poor because of previous thrombosis, there would occur such symptoms as confusion psychoses, mental changes, convulsions, aphasia, hemiplegia, paresthesias, delirium, and coma. The spinal fluid in such cases would be bloody under increased pressure and would contain excess protein and inflammatory cells. In acute lesions involving areas of previous injury, however, there may be obliteration of the subarachnoid space at the site of lesion by organized fibrous tissue, and in such lesions the lumbar spinal fluid would be normal or would show minimal changes.

The dilated vessels, the occasional hemorrhages, and the edema of the fundi, the localized facial swelling, the dilated and thickened and tortuous temporal vessels, the bulging fontanelles, and the epistaxis and relief of headache following epistaxis are clinical observations which indicate that cerebral stasis is present.

The severe pains in joints and bones which patients with sickle-cell anemia so commonly have are probably due to vascular lesions, inflammatory reaction, and irritation of nerve endings in these tissues. Some of the severe back pains and stiffness of the neck which may be interpreted as meningeal in origin may, in fact, be articular in origin or due to lesions in tendons and muscles. Some of the severe chest and abdominal pains and pains in the skin and in the extremities resemble the root pains such as are observed in tabes dorsalis and other spinal diseases[25] and are probably referred pains which are primary in the central nervous system or spinal ganglia. Laparotomies have been performed in patients with sickle-cell anemia during acute abdominal crises, and no gross lesions were found in the abdominal viscera.

The treatment of uncomplicated sickle-cell anemia is unsatisfactory, and there is no specific therapy. Following major vascular accidents and degenerative lesions there is nothing that can be done. Heparin, because of its antithrombotic value, vasodilators such as alcohol, nitroglycerin, and acetylcholine, and transfusion with blood plasma and ample fluids would be forms of rational therapy in early lesions. Carbon dioxide as a vasodilator would be contraindicated. Oxygen has been tried and apparently does no good.

SUMMARY

Central nervous system involvement is a frequent occurrence in sickle-cell anemia.

Reports of six new cases, two with autopsy, are presented, and the available literature including twenty-five other cases is reviewed.

The clinical manifestations and spinal fluid findings are summarized.

The essential pathology in the brain in sickle-cell anemia is similar to the pathology in other organs. The lesions are multiple and widespread but are mainly localized in the peripheral cortex and meninges. We consider the lesions to be primarily intravascular and due to thrombosis, following which there are extension of the thrombotic process and hemorrhagic, degenerative, and atrophic changes.

Prognosis is poor, but variable and unpredictable.

No effective form of treatment has been found.

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1417 HARBERT AVENUE

PHLYCTENULAR CONJUNCTIVITIS

Quantitative Details of Desensitizing Treatment in Sixteen Children

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THE principle of desensitizing treatment in phlyctenular conjunctivitis has long been recognized. The danger of focal and general reaction is such that many have feared or discarded it. We are showing in this series of sixteen cases that reactions can be minimized and avoided by determination of the skin threshold to tuberculin before starting treatment, and by beginning with a smaller amount of tuberculin than gives a positive skin test.

The children included in this report have had phlyctenular conjunctivitis as one manifestation of a tuberculous process. Each child has been studied as to the level of skin sensitivity to Koch's old tuberculin and then subjected to a series of injections of a desensitizing nature, starting with an amount below this level of sensitivity and small enough to avoid reaction of a local, focal, or general nature. The variation in severity of conjunctival irritation and erosion was extreme, some children showing one phlyctenule, others multiple ulcers. The response to treatment varied, we believe, because of the differing amounts of tuberculin circulating in the blood stream, liberated by the tuberculous processes elsewhere, and because of the differing allergic or sensitivity tendency of each child.

Table I gives the clinical description of these children in an abbreviated form. Their ages varied from 2 to 11 years; nine were negro children; all showed at least a childhood tuberculous process in the chest. The amount of local irritation of the conjunctiva varied from mild to severe, severe enough, in fact, to indicate enucleation in Case 16. Two had had tonsillar removal without effect upon the eye lesion, and five had history of previous eye inflammation. The details of treatment are abbreviated in Table II where the exact threshold dose of tuberculin, or the smallest amount to elicit a reaction, is recorded. These amounts vary from 0.001 mg. O.T. to 0.0000001 mg. O.T. and give a graphic idea of the extreme sensitivity to old tuberculin present in this group. It was seldom possible to keep these patients under treatment as long as would be beneficial, and we were forced to be content with shorter periods. The number of treatments to be given is variable and should be enough to reach at least 0.1 mg. O.T. Many patients could not be

From the Henry Ford Hospital.

TABLE I

CLINICAL DESCRIPTION OF CASES

CASE	ADMISSION DATE	AGE	SEX	RACE	FAMILY EXPOSURE	TUBERCULOUS PROCESS	DURATION BEFORE ℞	PHOTOPHOBIA	LACRIMATION	PURULENT DISCHARGE	PAIN	CONJUNCTIVA AND CORNEA			COMMENT
												INJECTION	PHLYCTENULE	ULCER	
1. E. T.	11/ 2/33	3	F	N	Yes	Active primary	2 days	Moderate	Moderate	None	Moderate	Yes	Yes	No	Tonsillectomy and adenectomy, 11//235
2. B. J.	3/26/35	8	F	W	Yes	Healed primary	2 wk.	Moderate	Moderate	None	None	Yes	Yes	No	
3. S. L.	4/30/35	6	F	W	Yes	Active primary	1 day	Severe	Severe	Severe	Severe	Yes	Yes	No	
4. O. T.	5/10/33	6	F	W	Unknown	Healed primary	2 wk.	Slight	Slight	None	Severe	Yes	Yes	No	History of one previous attack
5. J. W.	8/11/33	4	M	N	Unknown	Bone; active primary	4 wk.	Severe	Severe	Severe	Severe	Yes	Yes	No	Scars present from previous attack
6. W. J.	3/ 5/38	4	M	N	Yes	Active primary	3 wk.	Severe	Severe	Severe	Moderate	Yes	Yes	No	History of previous attacks
7. E. S.	3/25/38	8	F	N	Yes	Active primary	8 wk.	Severe	Severe	Severe	Moderate	Yes	Yes	Yes	Tonsillectomy and adenectomy 6/11/38
8. G. B.	5/ 2/38	6	M	W	Yes	Active primary	8 wk.	Severe	Severe	Severe	Severe	Yes	Yes	Yes	History of previous attacks

9. D. B.	6/20/38	4½	F	N	Unknown	Healed skin and cervical glands (primary)	6 wk.	Severe	Severe	Severe	Severe	Yes	Yes	Yes	
10. C. S.	6/20/38	2	M	N	Yes	Healed primary; cervical glands and skin	3 wk.	Mild	Mild	Mild	Mild	Yes	Yes	Yes	
11. H. S.	6/20/38	5	M	N	Yes	Active primary	12 wk.	Severe	Severe	Severe	Severe	Yes	Yes	No	Tonsillectomy and adenectomy 8 weeks before admission
12. A. G.	2/22/39	3	F	W	Yes	Active primary	2 days	Mild	Mild	None	Mild	Yes	Yes	No	
13. A. R.	6/10/39	7	F	N	Yes	Active primary	5 mo.	Severe	Severe	Severe	Severe	Yes	Yes	No	History of three previous attacks; Eye trouble one-half the time for 4 yr.
14. H. C.	7/28/39	8	F	N	Yes	Active primary	11 mo.	Severe	Severe	Severe	Severe	Yes	Yes	Yes	
15. J. W.	1/13/33	4	M	W	Yes	Healed primary	Few mo.	Severe	Severe	Mild	Severe	Yes	Yes	Yes	Tonsillectomy and adenectomy; non-tuberculous
16. F. P.	4/ 2/36	11	M	N	Unknown	Healed primary; skin	3 yr.	Severe	Severe	Severe	Severe	Yes	Yes	Yes	Left eye enucleated; Path. Exam. Phlyc. keratitis

TABLE II

DETAILS OF DESENSITIZING TREATMENT

CASE	SMALLEST AMT. O.T. GIVING SKIN REACTION (MG.)	TIME UNDER TREATMENT	NO. OF TREATMENTS	AMT. O.T. INJECTED SUBCUTANEOUSLY (MG.)		REACTIONS	ACUTE INFLAMMATION DISAPPEARED	TIME UNDER OBSERVATION	VISION AT DISCHARGE	COMMENT
				SMALLEST	LARGEST					
1. E. T.	0.0001	3 wk.	2	0.00001	0.0001	None	3 wk.	1 yr.	Good	Process gone
2. B. J.	0.0005	3 wk.	5	0.000001	0.1	None	3 wk.	2 mo.	R. 6/8 L. 6/12	Process gone
3. S. L.	0.0001	3 wk.	6	0.00001	0.0001	1	3 wk.	4 yr.	Good	No recurrence
4. O. T.	0.001	4 wk.	8	0.0001	0.01	None	4 wk.	8 mo.	Good	No recurrence; acute inflammation gone in 4 wk.
5. J. W.	0.000001	8 wk.	14	0.0000001	0.00007	1	6 wk.	12 mo.	Good	No recurrence; acute inflammation gone in 6 wk.
6. W. J.	0.000001	7 mo.	32	0.00000001	0.01	6	3 wk.	19 mo.	Good	No recurrence; acute inflammation gone in 3 wk.
7. E. S.	0.000001	7 mo.	16	0.00000001	0.000001	3	5 wk.	24 mo.	Good	Acute inflammation gone in 5 wk.
8. G. B.	0.000001	4 wk.	6	0.00000001	0.000002	1	4 wk.	8 wk.	Good	Bilateral gray scars still present
9. D. B.	0.0000001	22 mo.	51	0.00000001	0.6	4	Still present	22 mo.	Poor	Photophobia still present; process still active
10. C. S.	0.0000001	14 wk.	22	0.00000001	0.0007	1	3 wk.	22 mo.	Good	
11. H. S.	0.0000001	11 wk.	17	0.00000001	0.0001	2	4 wk.	20 mo.	Good	Acute inflammation gone in 4 wk.
12. A. G.	0.00001	6 mo.	27	0.0000001	0.5	2	3 wk.	8 mo.	Good	
13. A. R.	0.0000001	4 mo.	6	0.000000001	0.0005	None	6 wk.	4 mo.	Good	
14. H. C.	0.001	8 mo.	8	0.0001	0.04	None	Still present	8 mo.	Poor	Process still active
15. J. W.	0.000001	8 wk.	5	0.000001	0.01	2	8 wk.	8 wk.	Good in right	
16. F. P.	0.00001	3 mo.	11	0.00000001	0.00001	3	8 wk.	8 wk.	Good in right	

desensitized to this level because of reactions, and others failed to cooperate fully. When a reaction was encountered, the dose injected was lowered and then gradually increased again until a true desensitization was achieved. Seven have been under observation more than seven months. The vision was usually good at discharge. Abstracts on three patients follow, to show the exact method of applying the sensitization regime. In all cases, a high caloric, high vitamin C and vitamin D intake has been secured. The diet has included a large amount of milk, meat, and colored vegetables, and many of the children have required bed rest also. Atropine has been used locally as ointment or as drops to secure dilation of the pupil in the acute phase.

CASE 2.—B. J., an 8-year-old white girl, was admitted March 26, 1935, with the complaint of sore, painful eyes. The father was tuberculous, the child's chest x-ray showed a healed childhood lesion, and the Mantoux test was positive. Locally the eyes showed moderate photophobia, spasm, and lacrimation. The left cornea showed an opacity with an area of piled-up epithelium and severe keratitis. There were marked irritation and injection of the entire conjunctiva. The threshold of sensitivity was sought by varying intradermal tests as follows:

March 27—0.0001 mg. O.T., 0.00001 mg. O.T., and 0.000001 mg. O.T., of which all were negative.
March 30—0.001 mg. O.T. was given and proved positive.
April 4—0.0005 mg. O.T. was given subcutaneously.
April 9—0.001 mg. O.T.
April 12—0.002 mg. O.T.
April 15—Intradermal tests were repeated with 0.001 mg. O.T. and 0.01 mg. O.T., which were negative, and with 0.1 mg. O.T., which was positive.

At this time vision was: right, 6/7.5, and left, 6/12. Scarring in the left eye could be demonstrated only with the slit lamp. This patient represented the slightest or least type of case in which the diagnosis could be supported, and she responded well in five treatments. No further treatment was given.

CASE 6.—W. J., a 4-year-old negro boy, was admitted March 5, 1938, with the complaint of inflamed eyes. There was a history of exposure to a tuberculous uncle and of a previous attack of eye trouble in 1936. His chest x-ray showed active childhood infection with consolidation of the base of the left lung and hilus enlargement, and his Mantoux test was positive. The eyes had become inflamed in February, 1938, and showed severe photophobia, spasm, tearing, purulent discharge, and pain. The right eye showed a diffuse cloud over the cornea and a red, thick conjunctiva; the left, a large central opacity and general inflammation. His sensitivity was studied March 6, 1938, and he reacted to 0.001 mg. O.T. but failed to react to 0.0001 mg. O.T. intradermally. Subcutaneous injections were given as tabulated. With each local reaction the amount of old tuberculin given was lowered.

3/ 9/38	0.0001 mg. O.T. subcutaneously	
3/13/38	0.0004 " " "	Eyes improving
3/17/38	0.0007 " " "	Sclerae clear
3/21/38	0.001 " " "	
3/25/38	0.004 " " "	
3/29/38	0.007 " " "	
4/ 2/38	0.01 " " "	Eyes well healed. Local inflammation gone.
4/ 6/38	0.04 " " "	Marked local reaction at site of injection. Two patches of infiltration remained 1 mm. in diameter in lower left quadrant of cornea
5/ 3/38	0.0001 mg. O.T. intracutaneously	Reaction
5/10/38	0.00001 " " "	Reaction

5/17/38	0.000001	mg.	O.T.	intracutaneously	Reaction
5/30/38	0.00000001	"	"	"	Reaction
6/ 6/38	0.00000001	"	"	"	Reaction
6/19/38	0.0000001	"	"	subcutaneously	
6/30/38	0.0000001	"	"	intracutaneously	
	0.000001	"	"	"	Reaction
7/ 5/38	0.0000004	"	"	subcutaneously	
7/22/38	0.000001	"	"	"	
7/29/38	0.000004	"	"	"	
8/ 5/38	0.000007	"	"	"	
8/11/38	0.00001	"	"	"	
8/18/38	0.00004	"	"	"	
8/25/38	0.00007	"	"	"	
9/ 1/38	0.0001	"	"	"	
9/ 8/38	0.0004	"	"	"	
9/16/38	0.0007	"	"	"	
9/28/38	0.001	"	"	"	
10/ 4/38	0.004	"	"	"	
10/10/38	0.007	"	"	"	
10/18/38	0.01	"	"	"	

At the end of this course of treatment he had a small puffy scar in the lower left quadrant of the cornea. He has remained under observation for nineteen months, without recurrence. His desensitization was stopped at 0.01 mg. O.T. because of the extreme sensitivity formerly showed and the danger of more severe reactions. This is a sample of a moderate case which responds well but has a tendency to reaction, and which must be watched constantly to avoid a severe focal reaction in the eye itself.

CASE 9.—D. B., a 4½-year-old negro girl, was admitted June 20, 1938, complaining of most severe and constant pain in the eyes. There was a history of previous tuberculous cervical adenitis; a chest x-ray showed calcified hilar glands and a number of tuberculides, and the Mantoux test was positive. The eye inflammation developed six weeks before admission and consisted of severe photophobia and spasm causing her to keep her head buried, severe lacrimation, and constant purulent discharge. Under a general anesthetic (avertin) the eyes were examined, and the entire cornea of each eye, including the area over the pupil, was studded with round areas of piled-up epithelium and punctate opacities. There was extreme inflammation and cloudiness. Her sensitivity was studied, and she was treated as follows:

6/20/38	0.00000001	mg.	intradermally	Neg.	
	0.0000001	"	"	Pos.	
6/23/38	0.00000001	"	subcutaneously	Neg.	Temperature 100° in 60 hr.
6/29/38	0.00000001	"	"	Neg.	Temperature 99.6° in 60 hr.
7/ 3/38	0.00000003	"	"	Slight	Temperature 101° in 60 hr.
7/ 8/38	0.00000001	"	"	Neg.	
7/13/38	0.00000001	"	"	"	
7/18/38	0.00000003	"	"	"	Temperature 100.2° in 60 hr.
7/23/38	0.00000007	"	"	"	
7/29/38	0.0000001	"	"	"	
9/ 3/38	0.00005	"	"	"	
9/10/38	0.00005	"	"	"	
9/15/38	0.0001	"	"	"	
9/19/38	0.0002	"	"	Slight	
9/20/38	0.0002	"	"	Neg.	
9/26/38	0.0002	"	"	Slight	Marked improvement in symptoms
9/27/38	0.0002	"	"	Neg.	
10/ 4/38	0.0002	"	"	"	
10/15/38	0.00001	"	"	"	
11/ 3/38	0.00005	"	"	"	
11/28/38	0.00005	"	"	"	
12/ 3/38	0.0001	"	"	"	
12/12/38	0.0001	"	"	"	
12/19/38	0.0003	"	"	"	
1/ 5/39	0.0003	"	"	"	
1/16/39	0.0001	"	"	"	Return of phlyctenular conjunctivitis caused drop to .0001 mg.
1/24/39	0.0001	"	"	Pos.	Listless and will not eat; temperature 101°. Complains of arm where injection was given yesterday; large, firm, red area here
3/18/39	0.0000001	"	"	Neg.	
3/25/39	0.0000003	"	"	"	
4/ 6/39	0.0000005	"	"	"	Eyes rather severe; also put on ½% atropine oint.

4/11/39	0.0000005	mg. subcutaneously	Neg.	
4/17/39	0.0000008	" "	"	
4/22/39	0.000001	" "	"	
4/26/39	0.0000005	" "	"	
4/30/39	0.0000009	" "	"	
5/ 5/39	0.00003	" "	"	
5/10/39	0.00006	" "	"	
5/15/39	0.0001	" "	"	
5/20/39	0.0004	" "	"	
5/25/39	0.0007	" "	"	
6/ 1/39	0.001	" "	Pos.	
6/15/39	0.0007	" "	Neg.	
6/19/39	0.001	" "	"	
6/24/39	0.003	" "	"	
7/ 6/39	0.001	" "	"	Eyes much better; "some granulation tissue"
7/12/39	0.004	" "	"	
7/21/39	0.01	" "	"	
7/29/39	0.1	" "	"	
8/ 4/39	0.2	" "	"	
8/11/39	0.3	" "	"	
8/18/39	0.4	" "	"	
8/25/39	0.5	" "	"	
9/ 8/39	0.6	" "	Pos.	Temperature 102°. All inflammation gone. White scars at limbus of both eyes. Still slight photophobia
9/21/39	0.5	" "	Pos.	
9/29/39	0.3	" "	Neg.	
10/ 5/39	0.4	" "	"	

This was a sample of the most severe and resistant type which finally responded after more than a year of injections. I feel that this girl was producing a varying amount of tuberculin herself from other lesions, which, at times, accounted for her severe reaction.

COMMENT

Much experimental work has been done on this problem, and no attempt to name many valuable studies can be made. Our purpose in publishing these records is to emphasize the time and detail concerned in desensitization, the variation in the clinical picture presented, the ease of cure in some, and the failure in others. A detailed and scholarly exposition of the theory and application of the desensitization concept is contained in articles of Woods,[1-4] who has shown that the allergic or sensitivity reaction is a necrotizing tissue-destroying type of reaction, specifically dangerous in this condition, and that cutaneous and ocular sensitivities in an animal systemically infected run a remarkably parallel course. Gay[5] has worked out in detail practical directions in the use of this type of treatment for adults, but has no data concerning the greater sensitivity of children. King,[6] after his voluminous review, felt certain that tuberculin desensitizing treatment often saved the vision and must be used in this type of case. The experimental work to answer the question of how a phlyctenule is produced has shown that it is an allergic phenomenon, that this lesion can occasionally be produced by sensitivity to many proteins, that it can most often be produced in tuberculous animals, and that certain procedures such as injection of full strength old tuberculin or living tuberculous bacilli into the anterior chamber of sensitized animals may produce a phlyctenule.[2] In this connection it is to be remembered that the sensitivity of a child in the active phase of juvenile tuberculosis is not simply a plus or minus affair, but an extremely variable and delicate reaction,

as previously shown by the authors.[7] It is probable that the surprising cases of phlyctenulosis shown by Marfan[8] occurred in children in an extreme phase of sensitivity which is a characteristic of these patients, and agrees very well with the observation of Rich and McCordock[9] that lesions are favored by the virulence and number of infecting organisms and the increasing degree of allergy, and are counteracted by powers of general resistance and decreasing degrees of allergy. In our experience, the acute inflammation subsided in these acute conjunctival irritations in from three to six weeks, and in nearly all cases the patient progressed to a state of good vision. The sensitivity in most children is extremely high, but, where the skin threshold of reaction was low, as in Cases 4 and 14 who reacted to 0.001 mg. O.T., no reaction was encountered in starting desensitization injections at 0.0001 mg. O.T.

SUMMARY

Details of treatment of sixteen cases of phlyctenular conjunctivitis are given.

It is important to determine the smallest amount of tuberculin to which the patient will give an intradermal reaction and to start desensitizing injections below this point.

If reactions are encountered either locally at the site of injection or at the focus of infection, or generally, with rise of temperature, the amount of tuberculin must be lowered again.

In most cases acute inflammation can be overcome in from three to six weeks and sight can be restored, except for an occasional corneal scar.

Repeated examination of these children has been done by Dr. Whitney and Dr. Gemeroy of our Ophthalmologic Division.

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SPOROTRICHOSIS

Report of a Case

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Durham, N. C.

BECAUSE of the rarity of sporotrichosis in the South and the few cases of the disease reported in children, this case is reported in in detail.

CASE REPORT

M. H. (No. A27054), a 7-year-old white girl, was admitted to the Duke Hospital on Sept. 12, 1939, complaining of her left thumb which had been sore for two weeks.

The family history was irrelevant, except that the mother received anti-syphilitic therapy.

Past History.—Negative, except for report of occasional convulsions since the age of 3 years. Repeated Wassermann tests taken in the last year were reported as negative.

Present Illness.—In the latter part of August, 1939, three weeks before admission, she noticed a "pimple" on the left thumb, which her aunt pricked. (One week before this, she had played with a dead rat.) One week later the left thumb swelled and became red and tender, draining small amounts of thick, yellow-green material. On Sept. 1, 1939, five days after onset, she noticed "knots" appearing up the forearm and arm. These persisted to the time of admission. There had been no fever and no systemic symptoms.

Physical Examination.—The temperature was 37.4° C. (99.3° F.), pulse 100, respiration 20. The patient did not appear ill. There were palpable, nontender, anterior cervical nodes, and below the right temporomandibular joint there was a nodule of 2 cm., which was nontender and freely movable. The tonsils were large and cryptic. On the distal phalanx of the left thumb there was a shallow ulcer of 2 cm., covered with a yellow-green crust (Fig. 1). The surrounding tissue was red, tender, and swollen. Extending up the flexor surfaces of the left forearm and upper arm, there were successive nontender, freely movable swellings about 2 cm. in diameter (Fig. 2). These appeared to be distributed along the lymphatic channels.

Accessory Clinical Data.—The hemoglobin was 14.6 Gm. (94 per cent Sahli); red blood cell count, 4,980,000; white blood cell count, 10,450, with 47 per cent polymorphonuclear cells, 13 per cent eosinophiles, 1 per cent basophiles, and 37 per cent small lymphocytes. Urine and stool examinations and repeated Wassermann tests were negative. Dark-field preparation of material from the primary lesion revealed no spirochetes. There was no agglutination of *Pasteurella tularensis* antigen with the patient's serum.

Biopsies of the primary lesion and nodes in the left forearm were made for section and culture. Microscopic sections of the primary lesion on the thumb showed infiltration of the dermis with polymorphonuclear leucocytes and round cells. Microscopic sections of the forearm node showed a dense cellular infiltration, the cells being both chronic and acute inflammatory in type. No bacteria or fungi could be identified in stained sections.

From the Department of Pediatrics of Duke University School of Medicine and Duke Hospital.

Fig. 1.—Photograph showing primary ulcer on the dorsum of the thumb.

Fig. 2.—Photograph showing subcutaneous nodules extending up the arm.

A portion of the node taken at biopsy was ground in a mortar with saline, and three slants of Sabouraud's medium were inoculated.* After six days a small white growth, which later turned black, appeared on one of the slants. This growth was identified as *Sporotrichum schencki* (Fig. 3). There was no growth on the other two slants.

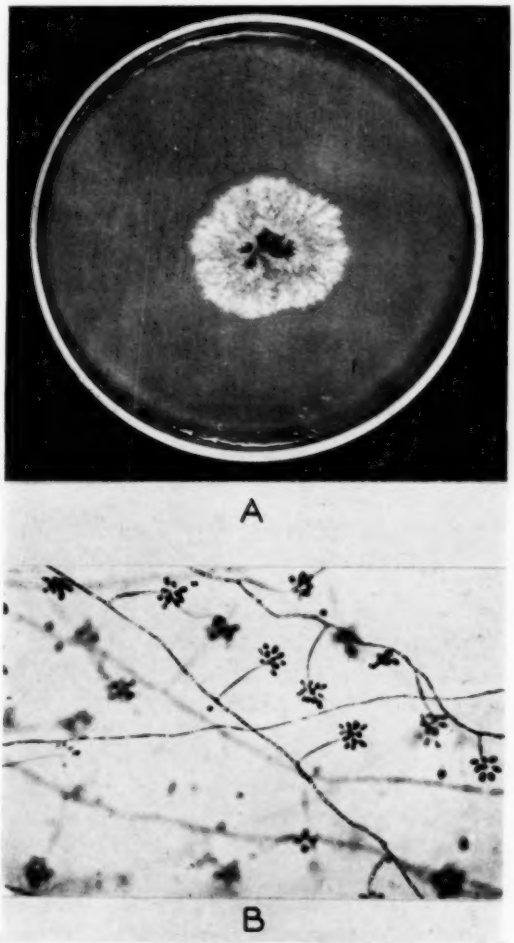

Fig. 3.—*A*, Photograph of culture taken from subcutaneous nodule; *B*, Photomicrograph of culture shown in *A*.

Course.—On Sept. 17, 1939, the sixth hospital day, the patient was given saturated (100 per cent) solution of potassium iodide three times daily, starting with a dose of 8 drops and increasing each succeeding dose by 1 drop. Saline compresses were applied to the thumb. Her condition was unimproved for the next eleven days; on September 28 and succeeding, the dose of potassium iodide was increased by

*Courtesy of Dr. N. F. Conant and Dr. D. S. Martin.

5 drops, and on October 4, she was receiving 100 drops three times daily, a dose which was continued. Three days after this dose was reached, the nodules could be detected only by palpation. The nodules below the right ear had almost disappeared. She was discharged on Oct. 7, 1939, and instructed to take 100 drops of potassium iodide three times daily. On Oct. 23, 1939, all of the nodules had disappeared, and the lesion on the thumb was healed.

DISCUSSION

Tularemia was considered as a possible diagnosis, but the afebrile course, lack of systemic reaction, and negative agglutination against *P. tularensis* made it unlikely. Syphilis was eliminated because of negative dark-field preparations of the chancre and repeated negative Wassermann tests. Low-grade pyogenic infection would not respond so dramatically to iodides.

It is of importance to note that diagnosis was not possible in this case by microscopic sections or direct examination of material taken from the primary lesion, but was made only by culture of the biopsy material, with inoculation of several slants.

BRONCHIECTASIS FOLLOWING ATELECTASIS IN TUBERCULOSIS OF INFANCY

Role Played by Enlarged Glands and Granulation Tissue

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TRACHEOBRONCHIAL obstruction caused by enlarged, tuberculous, hilar glands is a well-known, although relatively uncommon, clinical entity. It is the purpose of this paper to report a case in which enlarged tracheobronchial glands produced atelectasis and bronchiectasis within the first six months of life, and to record a second case in which the evidence suggests strongly that a similar mechanism was at work. In addition, a review of the literature dealing with atelectasis and bronchiectasis in tuberculous children is presented.

Tuberculous hilar glandular enlargement may interfere with respiration in a variety of ways. By simple external compression, the bronchial lumen may be partially narrowed or completely stenosed. The tuberculous gland may ulcerate through the bronchial wall, rupture into the lumen, and produce acute asphyxiation which may be immediately fatal. In the event of recovery from such an episode, there may remain a mural mass of tuberculous granulation tissue, either partially or completely occluding the airway. And finally, tuberculous cicatricial stenosis of the bronchus may result, producing a chronic interference with respiration, either by partially or completely shutting off the bronchus. With any of these various types of bronchial obstruction, the additional factor of thick, viscid, purulent, obstructive secretions may coexist and play a part in bringing about the interference with respiration.

Considered from a mechanical viewpoint, tuberculous hilar glands may produce two types of bronchial obstruction, partial and complete. Partial stenosis results from external compression, mural granulation tissue, or cicatricial contracture; complete stenosis results from any of these three factors, and from rupture of caseous glands into the lumen. That thick bronchial secretions may stop up the lumen has been mentioned already.

When partial obstruction reaches a stage where only a narrow chink of lumen remains, air is able to enter the area of lung supplied by the bronchus, but is unable to leave freely. Such trapping of air distal to a point of partial bronchial obstruction is called obstructive pulmonary emphysema. As Jackson has shown,[1, 2] such a situation develops because the bronchial lumen is larger on inspiration than on

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expiration; thus, a partial obstruction interferes with expiration before it does with inspiration. Also, inspiration is a more forcible process.

When obstructive pulmonary emphysema is present, there are diminished respiratory excursion and hyperresonance of the involved side of the chest; decreased or absent breath sounds on the involved side, with or without a wheeze; and displacement of the heart and mediastinum to the opposite side. On the involved side the roentgenogram shows diminished density, widening of the intercostal spaces, and depression of the diaphragm; in addition, it shows displacement of the mediastinal structures and the heart to the opposite side, with or without compression atelectasis on the opposite side.

Spivek[3] has recently reviewed the literature dealing with partial bronchial stenosis caused by tuberculous hilar glands, emphasizing particularly obstructive pulmonary emphysema.

When partial stenosis progresses to complete obstruction, a more severe degree of bronchial occlusion occurs, so that air is prevented entirely from passing the point of obstruction. The air trapped distal to the point of complete obstruction is absorbed, and the involved lung tissue shrinks and collapses, producing atelectasis.

When atelectasis is present, there is, at first, dullness and absence of breath sounds over the involved area. But, as the air in the alveoli is absorbed, consolidation occurs, producing the well-known signs of dullness, bronchial breathing, bronchophony, and shift of the heart toward the involved side, provided the atelectasis is extensive enough. A roentgenogram shows an area of increased density on the involved side, usually triangular in shape and located at the base of the lung, shift of the heart and mediastinal structures toward the involved side, elevation of the diaphragm and narrowing of the intercostal spaces on the affected side, and usually evidence of compensatory emphysema in the remaining portions of the lung.

If such an atelectasis is prolonged, bronchiectasis is prone to develop in the atelectatic area, for it has been repeatedly shown[4-7] that atelectasis predisposes to bronchiectasis. The two cases presented here, in our opinion, illustrate this final state in complete bronchial stenosis.

CASE REPORT

CASE 1.—M. D., a premature negro girl, was born Aug. 8, 1938, at the seventh month, weighing 3 pounds. No cause for her prematurity was found. The mother's Kahn test for syphilis was negative. The patient remained in the premature station of the John Gaston Hospital for two months, at which time she was discharged home in good condition, weighing 4 pounds and 6 ounces. No abnormalities were noted during her two months' hospitalization.

One month after her return home she began to have a paroxysmal cough, nasal discharge, and fever. Examination showed a poorly nourished baby with a paroxysmal cough, low fever, mucopurulent nasal discharge, and a mild pharyngitis. The chest seemed normal to examination. Routine blood and urine examinations were

normal, and the Kline test for syphilis was negative. A tuberculin test was not done. The child gained 7 ounces in one week and was then discharged home, improved, but continuing to have a slight cough.

She was readmitted to the hospital December 15, 1938, at the age of 4 months, because of an acute upper respiratory infection. In addition, a paroxysmal cough similar to that previously noted was present. It was thought that the cough was due to the acute respiratory infection. Again, a tuberculin test was not performed. The cough diminished, but did not subside completely. She gained steadily and was discharged, improved, two weeks after admission.

Her cough grew worse at home, and she began to have low fever. On February 2, 1939, she re-entered the John Gaston Hospital. She did not appear very ill, but had a frequent paroxysmal cough. There were coarse inspiratory râles over the entire chest except over the lower lobe of the right lung where there were dullness, bronchial breathing, and bronchophony. The heart seemed shifted to the right. The pharynx was moderately inflamed. The tuberculin skin test with first strength solution of purified protein derivative was strongly positive.

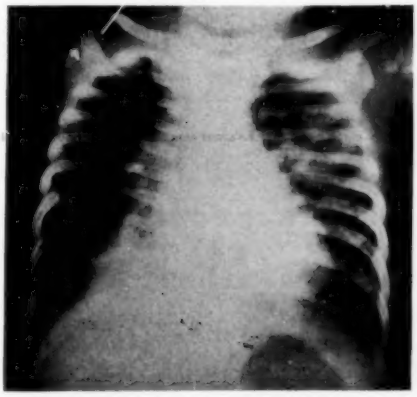

Fig. 1.—Chest roentgenogram of M. D., showing soft, mottled shadows in each lung field, and a sharply outlined triangular shadow at the base of the right lung. At autopsy the mottled shadows were found to be due to tuberculous bronchopneumonia, and the triangular shadow was produced by atelectasis of the right lower and right middle lobes.

The chest roentgenogram (Fig. 1) showed soft, mottled shadows in each lung field which were interpreted to represent areas of bronchopneumonic consolidation. There was a sharply outlined triangular shadow at the base of the right lung, which was considered indicative of atelectasis of the right lower lobe. In the right hilar region was a rounded shadow projecting into the right lung field, which was considered to represent tuberculous hilar glands. The clinical diagnosis at this time was: tuberculosis of the lungs, tuberculous bronchopneumonia, and bronchial stenosis due to tuberculous hilar glands, with atelectasis of the right lower lobe.

The child grew progressively worse. She coughed more and more frequently, but there was no noticeable bitonal quality to the cough such as Schick[8] has emphasized occurs in partial bronchial compression from enlarged hilar glands. The cough was characterized chiefly by paroxysmal and severe attacks. Constant, continued retraction of the suprasternal tissues, the lower rib margins, and the epigastrium set in, becoming progressively severe. On February 21, edema of the face and upper extremities appeared (Fig. 2), and within a day or two the whole body became swollen, but to a lesser extent than the face.

The child died Feb. 28, 1939, at the age of 5 months, two months after onset of symptoms referable to the respiratory tract.

A post-mortem bronchoscopic examination, performed by one of the authors (W. L. S.), revealed a markedly narrowed lumen of the right lower lobe bronchus, apparently from external compression. The mucous membrane was reddened and edematous. A considerable amount of purulent secretion welled out of the right main bronchus. No mural granulation tissue was seen.

Fig. 2.—Photograph of M. D., showing edema of face and upper extremities produced by obstruction of the superior vena cava by tuberculous mediastinal glands.

An autopsy was performed shortly after death by Dr. Harry Davis, who gave the following report of significant findings:

"Examination of the thoracic cavity (Figs. 3 and 4) revealed the presence of numerous enlarged mediastinal and hilar lymphatic glands, which upon section showed the presence of typical tuberculous caseation. The right main bronchus, at its junction with the trachea, showed an almost complete compression by an enlarged caseous lymphatic gland which appeared to be partially surrounding the wall. The bronchi and bronchioles leading from the compressed bronchus into the lower and middle lobes of the right lung showed definite bronchiectasis. There was present atelectasis of the right middle lobe and right lower lobe which was particularly seen along the posterior portion of the lower border.

"The remainder of the lung revealed tuberculous bronchopneumonia, but no evidence of bronchial obstruction or bronchiectasis.

"The superior vena cava, at a point 5 cm. from its entrance into the right auricle of the heart, showed a partial obstruction as a result of compression by enlarged caseous mediastinal lymphatic glands.

"The remainder of the autopsy revealed evidences of tuberculosis in the spleen, liver, and ileum.

"Microscopic examination confirmed the gross findings."

The lungs and heart were removed from the chest and roentgenograms were made with and without the use of contrast filling of the tracheobronchial passage with an opaque medium.

Fig. 3.—Gross appearance of lungs of M. D., showing atelectasis of right middle and right lower lobes and tuberculous bronchopneumonia in remaining portions of the lungs.

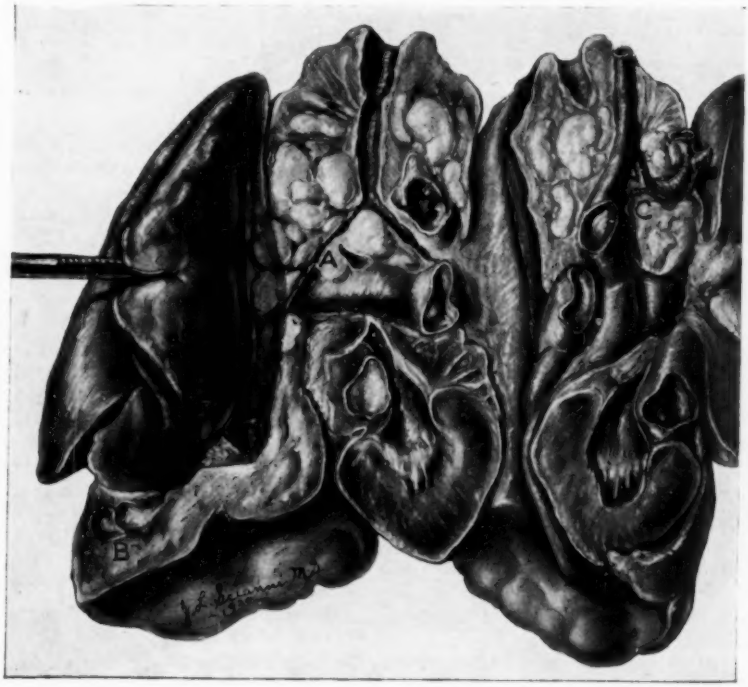

Fig. 4.—Drawing of section of lungs showing: (*A*) almost complete compression of bronchi to right middle and lower lobes by tuberculous hilar glands; (*B*) saccular bronchiectatic cavity in right lower lobe, distal to site of bronchial compression; and (*C*) marked compression of the superior vena cava by mediastinal tuberculous glands.

When iodochloral was poured into the tracheobronchial passages under atmospheric pressure, it descended into the left lower lobe bronchus, but failed to enter the bronchi to the right lower and right middle lobes (Fig. 5). The point of obstruction corresponded with the site of enlarged caseous tuberculous hilar glands found at autopsy, and also with the markedly narrowed lumen of the right lower lobe bronchus seen at post-mortem bronchoscopic examination.

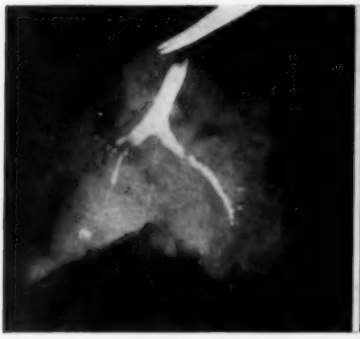

Fig. 5.

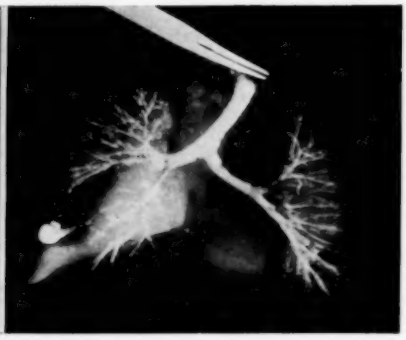

Fig. 6.

Fig. 5.—Roentgenogram of excised lungs of M. D., after iodochloral had been poured into the tracheobronchial tree under atmospheric pressure. The opaque medium failed to enter the bronchi to the atelectatic right middle and lower lobes, but descended into the bronchus to the left lower lobe.

Fig. 6.—Bronchogram of excised lungs of M. D., after forceful injection of iodochloral, showing marked stenosis of the right lower lobe bronchus and tubular and saccular bronchiectasis of the right lower and middle lobes.

A bronchogram taken after forceful injection of iodochloral into the tracheobronchial passages (Fig. 6) showed marked stenosis of the right lower lobe bronchus and tubular and saccular bronchiectasis of the lower and middle lobes of the right lung. The right upper lobe bronchi and all the bronchi in the left lung showed normal configuration.

CASE 2.—M. H., a well-developed and well-nourished 2½-month-old negro girl, was admitted to the John Gaston Hospital Dec. 6, 1938, because of a paroxysmal cough of three weeks' duration, accompanied by failure to gain weight. The day before admission she had coughed up bloodstreaked sputum. Her past history had been normal. However, the mother was known to have active tuberculosis of the lungs. On admission, the child had a paroxysmal croupy cough occurring every five to ten minutes and lasting from thirty to sixty seconds. Inspiration was rapid and short; expiration was prolonged and difficult. The pharynx was mildly inflamed. Fine, crackling, inspiratory râles were heard over the entire chest. No wheeze was noted. The tuberculin skin test with first strength solution of purified protein derivative was strongly positive. A Vollmer (Lederle) tuberculin patch test was also positive. Tubercle bacilli were not found in the gastric washings at this time, although the examination was made only once. A mild anemia existed.

The roentgenogram of the chest (Fig. 7) showed a large irregular right hilar shadow which was interpreted to represent a tuberculous process in the right lung and right hilar glands. There was no appreciable shift of the mediastinum.

The child improved slightly, and was discharged to the Tuberculosis Clinic on Dec. 12, 1938.

On Jan. 5, 1939, she was readmitted to the hospital at the age of 3 months because of severe dyspnea, paroxysmal cough, and failure to gain weight. She had suffered from dyspnea, especially at night, since her previous discharge from the hospital.

The child presented a picture of extreme respiratory difficulty. Expiration was prolonged and difficult and accompanied by a crowing noise; inspiration was shorter, noiseless, and relatively easy, although a moderate amount of retraction of the chest was present. The chest showed diminished respiratory excursion on the right, increased resonance to percussion on the right, and decreased breath sounds over the right lower lobe. It was difficult to locate the position of the heart, but it seemed to be displaced to the left. A to-and-fro wheeze was heard over the entire right lung and, to a less extent, over the left lung. It was the opinion that the child had obstructive right pulmonary emphysema caused by enlarged tuberculous hilar glands.

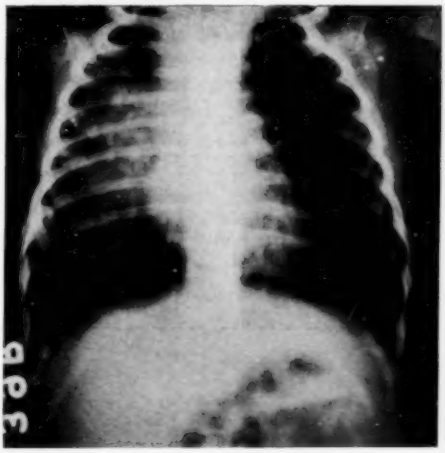

Fig. 7.—Chest roentgenogram of M. H., showing large, irregular right hilar shadow without mediastinal shift.

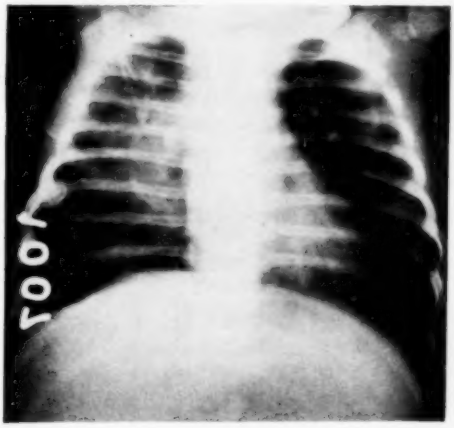

Fig. 8.—Chest roentgenogram of M. H., showing the findings of obstructive emphysema on the right side with displacement of the heart and mediastinal structures to the left.

The roentgenogram of the chest (Fig. 8) showed the findings of an obstructive pulmonary emphysema of the right lung and a large right parenchymal shadow

partially obscuring the signs of obstructive emphysema. The heart was displaced slightly toward the left, and the right leaf of the diaphragm was moderately depressed. Because of the right parenchymal shadow, it was difficult to judge the extent of aeration of the right lung.

Although the question of the advisability of x-ray therapy for tuberculous hilar glands is controversial, it was decided to try to reduce the size of the glands by this means. Only two treatments were given, three days apart, and consisting of 122 roentgens and 100 roentgens, at a voltage of 130 kv., 5 Ma., and with 3 mm. of aluminum filter. The distance of the tube was 15 cm., and the radiation was centered over the right anterior surface of the chest. It is questionable how effective such an amount of treatment could have been in reducing the size of the glands, but the dyspnea decreased moderately in severity. Since the child was improving, no bronchoscopic examination was done at this time.

Gradually the clinical signs of obstruction to respiration diminished, but did not disappear entirely. Whenever the child was handled, respiration became more difficult and the paroxysmal cough which was present throughout the illness became accentuated.

After the first few days, during which time the findings of obstructive pulmonary emphysema were present on the right, there developed a well-marked atelectasis of the right lower lobe. The right lower lobe became dull; bronchial breathing and bronchophony were heard in the base of the right lung posteriorly, and the heart seemed shifted to the right.

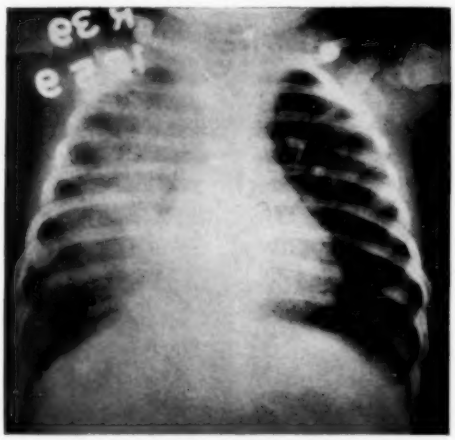

Fig. 9.—Chest roentgenogram of M. H., showing a triangular shadow in the right base, believed to be due to atelectasis of the right lower lobe.

A chest roentgenogram (Fig. 9) taken January 11, six days after admission, showed a dense shadow in the right base, triangular in shape and almost obscured by the heavy parenchymal shadow jutting out from the right hilum. The presence of this triangular shadow confirmed the clinical impression of atelectasis of the right lower lobe.

The child took its feedings poorly, failed to gain weight, and became weaker and weaker.

Tubercle bacilli were found in the gastric washings.

On March 1, 1939, two months after admission, a bronchoscopic examination was performed by one of the authors (W. L. S.). A large amount of purulent secre-

tion came from the right main bronchus, which seemed to be moderately compressed. The mucous membrane of the right bronchial passages was edematous and reddened. Iodochloral was injected into the right main bronchus. The roentgenogram taken after injection of iodochloral (Fig. 10) showed marked saccular and tubular bronchiectasis in the right lower lobe in the area where previously the triangular shadow had been noted.

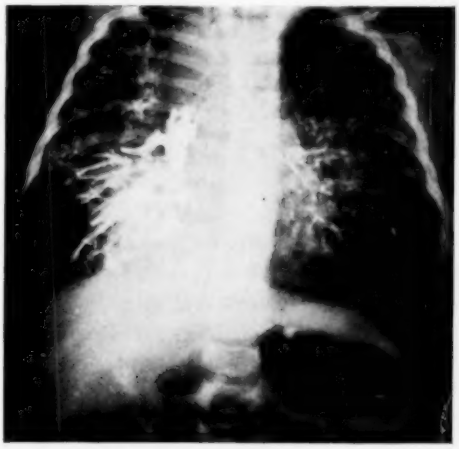

Fig. 10.—Bronchogram of M. H., showing marked tubular and saccular bronchiectasis in the atelectatic right lower lobe.

The child grew worse gradually, and she died March 15, 1939, at the age of 5 months, three months after the onset of symptoms referable to the respiratory tract.

Permission for autopsy was denied, but a post-mortem bronchoscopic examination was performed by one of the authors (W. L. S.). There was a considerable amount of thick gray pus welling out of the right main bronchus. The mucosa of the right bronchial passages was inflamed. Mural granulation tissue was found almost entirely occluding the lumen of the right lower lobe bronchus. A specimen of this tissue was obtained for examination. Dr. C. E. Gillespie gave the following report of the pathologic findings: "Microscopic examination of the tissue removed from the bronchus reveals irregular fragments of necrotic tissue partially surrounded by fibrous tissue. In some portions of the fibrous tissue, fibroblasts are fairly frequent, and a mild infiltration with small mononuclear cells is noted. An occasional giant cell of the Langerhans type is also seen, but there are no tubercle formations apparent. The necrosis is of the caseous type, and the structure of the tissue is completely destroyed in the necrotic areas. Appropriate stains fail to reveal any evidence of tubercle bacilli in the tissue. The histopathology of this tissue is not inconsistent with that of a tuberculous lesion."

It is admitted freely that the first case presented (M. D.) does not illustrate complete occlusion of a bronchus from external compression alone, but that the additional factor of thick, viscid, obstructive secretions must be accorded partial credit in the production of atelectasis and bronchiectasis. External compression plus edema of the mucous membrane and, finally, obstructive secretions must all have played their parts in producing the atelectasis and resultant bronchiectasis. How-

ever, obstruction of the lumen was almost complete from compression alone, as illustrated in the bronchogram (Fig. 6). It is felt that bronchography gives better evidence of the extent of compression than does gross examination of the lung at autopsy, because when a bronchus is cut open to inspect the lumen, the compression is immediately relieved and the bronchus spreads open, making a reliable estimation of the extent of compression difficult.

Bronchograms in the living subject are probably less accurate than are bronchograms of excised lungs where the opaque medium may be injected under pressure sufficiently great to outline the obstructed area. This fact is illustrated in the first case (M. D.) where iodochloral failed to pass the point of obstruction when poured into the tracheobronchial tree, but passed the point of obstruction, revealed the extent of occlusion, and demonstrated the distal bronchiectasis when injected under strong pressure.

The evidence that the second case (M. H.) illustrates bronchial obstruction from enlarged tuberculous hilar glands is necessarily equivocal because an autopsy was not permitted, but it is felt that all evidence short of an actual autopsy strongly indicated that such a mechanism was at work. First, the case had primary tuberculosis without bronchial obstruction, then partial bronchial obstruction with obstructive emphysema, then complete bronchial obstruction with atelectasis and bronchiectasis. The mother was known to be tuberculous, the tuberculin test was positive, and tubercle bacilli were found in the gastric washings. Granulation tissue was found in the bronchial lumen, but, unfortunately, biopsy did not conclusively prove the tissue to be tuberculous. Spivek has shown[3] that, following rupture of a tuberculous hilar gland into the bronchial lumen, mural granulation tissue may subsequently produce bronchial obstruction.

DISCUSSION

The clinical diagnosis of tracheobronchial obstruction from enlarged tuberculous hilar glands rests upon some or all of the following points: history of exposure to tuberculous infection, history of respiratory obstruction of a prolonged nature in infancy or childhood, positive tuberculin test, finding the tubercle bacilli in the sputum or gastric washings, roentgenographic evidence as brought out in the two cases presented, bronchoscopic examination with or without biopsy of tuberculous mural granulation tissue, and bronchography. The demonstration at physical examination of obstructive emphysema or of atelectasis should bring to mind the possibility, among other things, of enlarged hilar glands. As Petot has shown,[9] various physical signs formerly considered indicative of enlarged hilar glands are not reliable enough to be pathognomonic of mediastinal glandular enlargement.

No attempt will be made to estimate the frequency of atelectasis and bronchiectasis in tuberculosis of infancy and childhood. Suffice it to say that these conditions are relatively rare. Most of the reported cases of tuberculous atelectatic bronchiectasis have been in children past infancy and in young adults.

Lightwood and Wilson[10] reported the case of a 5-year-old boy who had partial stenosis of the left main bronchus and atelectasis and bronchiectasis of the left lung. The tuberculin test was positive, and a calcified gland could be seen in the left hilum on the roentgenogram. The authors concluded that the bronchial stenosis and resultant atelectasis and bronchiectasis might have been due to the effects of a caseous gland in the neighborhood of the left main bronchus or to an ulcerative tuberculous bronchial lesion.

Wilson[11] reported the case of a 6-year-old boy who had partial stenosis of the right lower lobe bronchus and atelectasis and bronchiectasis of the right lower lobe. Tuberculous mural granulation tissue was removed from the right lower lobe bronchus. The tuberculin test was positive. Spontaneous improvement occurred.

Jones and Cournand[12] recorded four cases of atelectasis and bronchiectasis which they believed were caused by bronchial stenosis from tuberculous glands. They were inclined to believe that, besides the stenosis of a bronchus from outside pressure due to congested lymph nodes, the loss of the normal bronchial function and the inflammation of the bronchial tree by infection from the lymph nodes were factors in the causation of bronchiectasis.

Boyd[13] reported in his discussion of bronchiectasis in children that "although our pathological museum boasts but few specimens of bronchiectasis, there are two in which tuberculous glands have caused the development of retention bronchiectasis."

Wallgren[14] reported the case of a girl who developed bronchiectasis at the site of a previous primary tuberculous focus, and he mentioned that he had seen seven other similar cases. He stressed the importance of destruction of the bronchial epithelium and bronchial wall and the contraction of peribronchial scar tissue in the etiology of such cases of bronchiectasis following tuberculous lesions in children. He gave no consideration to the factor of bronchial stenosis from enlarged tuberculous hilar glands with resultant retention bronchiectasis.

Eloesser[15] has treated in great detail the subject of bronchial stenosis in pulmonary tuberculosis among adult patients. He reported many instances of bronchiectasis following bronchial stenosis from tuberculous lesions, in some cases enlarged hilar glands. He stated[5] that compression and distortion of the lower trachea and bronchi from tuberculous glands have been repeatededly observed and that areas of bronchiectasis are rarely wanting in such lungs.

Ballon, Singer, and Graham[4] recorded no definite cases of tuberculous atelectatic bronchiectasis, but stated that "tuberculous peribronchial glands may either break into a bronchus or so narrow it as to produce dilatations beyond the point of narrowing."

Jackson and Jackson[16] reported three types of bronchial obstruction due to enlarged tuberculous hilar glands which occurred in an infant 20 months old. Eventual bilateral atelectasis was produced, with resultant death. Diagrams were presented to illustrate the mechanics of bronchial obstruction by tuberculous glands.

Anspach[6] stated that "narrowing of the lumen of the bronchus by enlarged glands, either by preventing drainage or by increasing the temporary intrabronchial pressure, has recently been regarded as a possible explanation for the development of bronchiectasis," but that no cases of this nature had been encountered in his series of patients with bronchiectasis. He emphasized[7] the role played by "an intrabronchial plastic material such as secretion or swollen membrane to complete the obstruction" partially produced by compressing glands. In his opinion,[17] decreased ability to evacuate the lung and retention of secretion in the bronchi of small diameter play a greater role in the production of atelectasis and bronchiectasis in these cases than does compression by enlarged hilar glands.

An interesting point about bronchial stenosis from tuberculous lesions is the predominance of involvement of the right lung. A probable explanation lies in the fact that, as Petot[9] has shown, the lymph nodes which are most frequently enlarged and exert pressure on the bronchi in the respiratory infections of childhood are those surrounding the right stem bronchus in proximity to the origin of the bronchus to the right middle lobe.

SUMMARY

Attention is called to tracheobronchial obstruction from enlarged tuberculous hilar glands.

The various mechanisms by which enlarged tuberculous hilar glands may cause tracheobronchial obstruction are discussed.

Two cases are presented in which such an obstruction seemed present, leading to atelectasis and bronchiectasis in the atelectatic area.

The second case (M. H.) illustrates, in our opinion, four phases of hilar glandular enlargement: (1) enlargement without bronchial compression; (2) partial bronchial stenosis with obstructive emphysema; (3) complete bronchial stenosis with atelectasis; and, finally, (4) tubular and saccular bronchiectasis in the atelectatic area.

The first case (M. D.) also illustrates compression of the superior vena cava by tuberculous mediastinal glands, causing marked edema of the head, neck, and arms.

A review of the literature dealing with atelectasis and bronchiectasis in tuberculous children is given.

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HYPERTENSION IN DIPHTHERIA

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THAT the blood pressure is often lowered in diphtheria is a well-known clinical observation, but the occurrence of the reverse phenomenon, hypertension, has rarely been reported. This is especially striking since numerous investigations have been made concerning the relation of blood pressure to the clinical course of diphtheria and its prognostic significance in this disease. During the past few years, several articles have appeared in the German literature on the occurrence of hypertension in diphtheria. So far as I have been able to determine, this fact has never been brought out previously in the English literature, except for two case reports in the recent article by Harrison and Williams.[1]

It is the purpose of this paper to present two cases of hypertension occurring in the course of postdiphtheritic paralysis. One of these cases from the Vanderbilt University Hospital was mentioned in the article by Harrison and Williams. The other case was followed in the Louisville City Hospital. In addition to the report of these two cases, a brief review of the literature on this subject and a discussion of the etiology will be presented.

CASE REPORTS

CASE 1.—S. C., white female, 7 years old, was admitted to the Vanderbilt Hospital on Dec. 22, 1937. Four days before admission she developed a sore throat with swelling of the glands on the left side of her neck. The following day, her tonsils and pharynx were covered with a white membrane, and she had bilateral swelling of the neck. Two days before admission, she was seen by a physician who gave her an intramuscular injection of 10,000 units of diphtheria antitoxin. On the following day, she received another intramuscular injection of 10,000 units.

On physical examination, the temperature was 102° F., pulse 100, respiration 24, weight 41 pounds, and blood pressure 120/80.

The patient was poorly nourished and poorly developed and appeared acutely ill. The tissues of her neck were swollen bilaterally, and her cervical glands were markedly enlarged. Over the uvula, tonsils, and posterior pharynx, there was a grayish-white membrane, and the entire pharynx appeared swollen. The rest of the examination was negative.

Positive laboratory findings revealed a throat culture positive for *Bacillus diphtheriae*. Urine showed a trace of albumin and occasional white blood cells, but repeated urinalyses failed to show casts or red blood cells.

Course.—On Dec. 31, 1937, nine days after admission, the child developed a rapid pulse and gallop rhythm, but the electrocardiogram was normal and there was no cardiac enlargement on physical or roentgenologic examination. By Jan. 12, 1938, the electrocardiogram showed some change compatible with myocardial disease. The gallop rhythm persisted for about two weeks, and there was never any evidence of myocardial failure.

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On Jan. 27, about six weeks after onset of the diphtheria, the child developed marked pharyngeal and laryngeal paralysis, such that she could not swallow. At about the same time, it was noted that she was developing an elevation of blood pressure ranging from 130/90 to 180/155. The nonprotein nitrogen and urine were normal. The deep reflexes became sluggish, but were never totally absent. Because

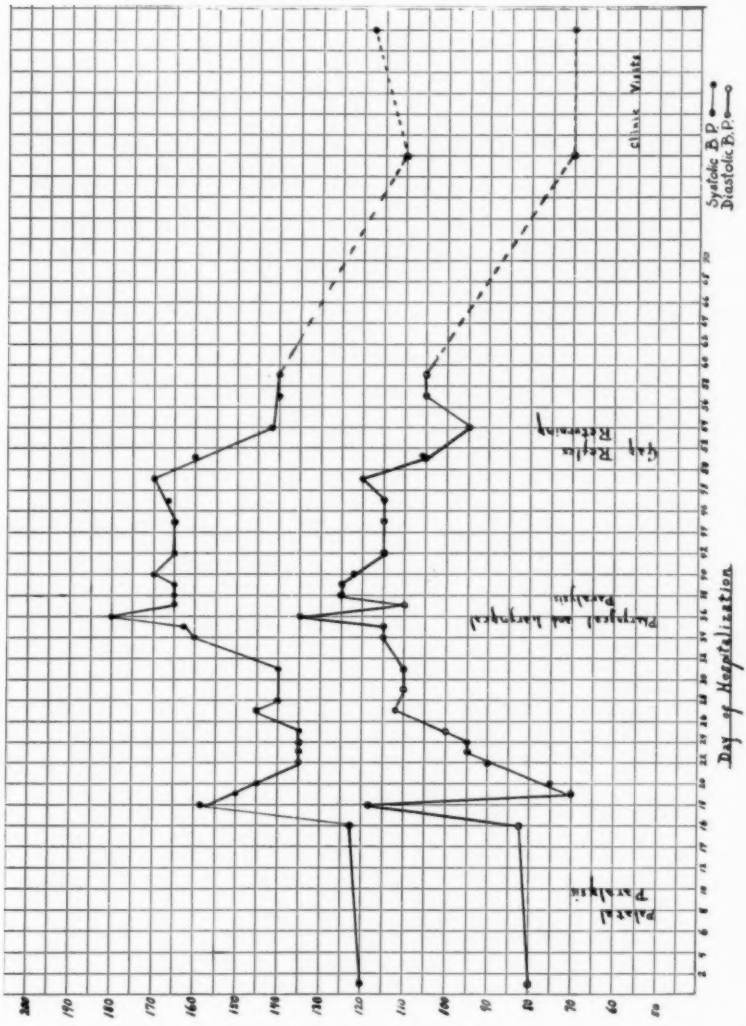

Chart 1.—Case 1, S. C.

of the paralysis of the muscles of swallowing, it was necessary to feed her by gavage for about three weeks, after which the gag reflex returned and she was able to swallow food without difficulty. At this time, it was noted that her blood pressure tended to drop to normal values. The hypertension developed with the onset of paralysis and tended to become less marked as the paralysis cleared. The

child returned to the clinic on March 5, at which time she was crying a great deal and her blood pressure was 160/110; examination of the urine revealed no abnormality. On April 2, her blood pressure was 110/70, with a normal urinalysis, and on August 20, the blood pressure was 118/70 (Chart 1).

CASE 2.—D. C., white female, 7 years old, was admitted to the Louisville City Hospital on Sept. 4, 1939. About three weeks prior to admission, she had had a sore throat and temperature of 104.6° F. A local physician found patches of yellow exudate over both tonsils. Sulfanilamide was administered, and it is reported that her throat was clear in twenty-four hours. No culture of the throat was taken. After a few days, the fever subsided, and the patient seemed well. One week prior to admission, she began to complain of weakness in her legs and she fell down on attempting to walk. About this time, she developed a nasal voice, and fluids were regurgitated through her nose. Three days previous to admission, she had fever, headache, and anorexia.

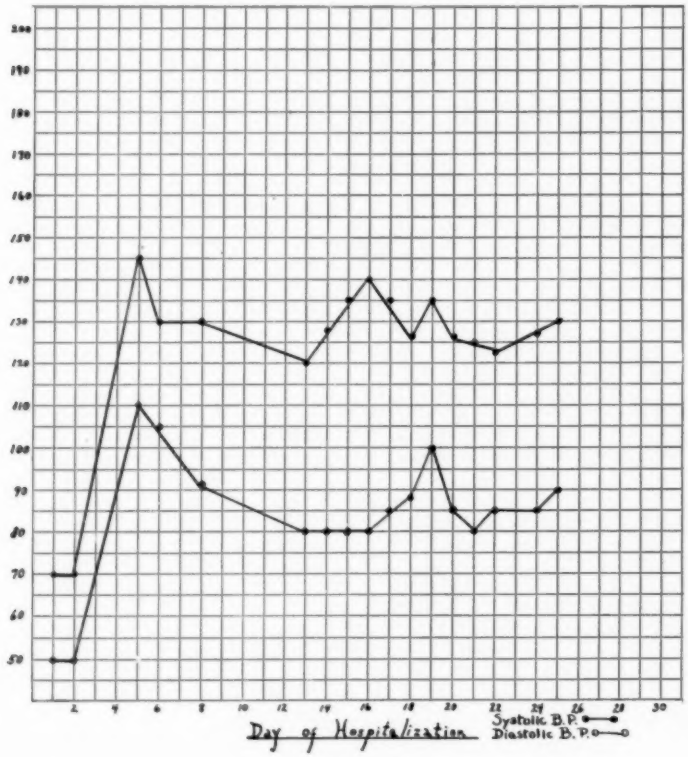

Chart 2.—Case 2. D. C.

Physical examination revealed a temperature of 99.6° F., pulse 120, respirations 24, and blood pressure, 70/50.

The patient was a poorly developed white girl who appeared moderately ill. Her physical examination revealed the following significant positive findings. There was internal strabismus of her left eye. She had a slight injection of the pharynx.

Her back was somewhat stiff, and she complained of pain on flexion of her back and thighs. Kernig's and Brudzinski's signs were positive, the knee and ankle jerks were absent, and abdominal reflexes were also absent. Her legs were flaccid, but the strength of her arms was normal.

Significant Laboratory Findings.—The Schick test was negative. The electrocardiogram was normal. Repeated throat cultures showed no Klebs-Löffler bacilli, and repeated urinalyses showed no abnormalities.

Course.—During her month of hospitalization, the patient's temperature was never elevated above 99.6° F., and her pulse ranged from 90 to 150 (mean, 100 to 120). Her blood pressure rose from 70/50 on admission to a maximum of 145/110 as the paralysis progressed and then tended to decrease as the paralysis cleared (Chart 2). The ability to use her extremities gradually improved, and the stiffness of her back subsided quickly. Although diagnosis could not be established definitely, it seemed possible that it was a case of postdiphtheritic paralysis.

The basic work on blood pressure in diphtheria was done in 1893 by Friedemann at Heubner's Institute in Leipzig.[2] Friedemann studied sixty-three cases of diphtheria, of which thirty were fatal. In all but one case, the blood pressure was normal or low. In 80 per cent of the fatal cases, the blood pressure first fell to the level that he considered critical (60 to 65 mm.) forty-eight hours before death. Biernacki,[3] Durand-Viel,[4] and Denis[5] concluded that a fall of pressure took place in every form of diphtheria, mild or severe, the fall being relatively more marked in older children and in severe forms of the disease.[6] Taddei,[6] Weigert,[7] and Bruckner[8] found that the blood pressure was normal in mild cases and was lowered in proportion to the degree of toxicity in the moderate and severe ones. Rolleston[9] and Fiedler[10] agreed with this, and found that the blood pressure was usually lowest during the second week of the disease, returning to normal by the seventh week.

In this early literature, reports of cases which showed hypertension are, with few exceptions, limited to patients with respiratory obstruction. Friedemann[2] reported a case of a 7-year-old girl whose blood pressure rose to 130 mm. with symptoms of respiratory obstruction and then dropped to 85 mm. with relief of the dyspnea. Rolleston,[9] Slatkow,[11] and Hensen[12] recorded similar cases. This agrees with the observations of Hensen that dyspnea increases blood pressure, and of Ziemssen[13] that in Cheyne-Stokes respirations, blood pressure climbs during the period of dyspnea. Kollosowa[14] found increased blood pressure with the appearance of albuminuria in eighteen patients in contradiction to Slatkow,[11] Taddei,[6] Denis,[5] and Rolleston who found a hypotension.

Von Kiss[15] was the first to note the occurrence of hypertension in uncomplicated cases of diphtheria. Unfortunately, he gave detailed figures on only a few of his patients, most of whom exhibited postdiphtheritic paralysis and are discussed below. Catel[16] followed the blood pressure in 215 diphtheritic children over 7 years of age. In 7 per cent of his cases, there was a hypertension maintained over a period lasting from a few days to several years. The increase varied from 10 to 30 per cent over his standard of 100 plus twice the age. Urinary findings were

essentially normal. Lutz[17] found a hypertension of brief duration in eight of his forty cases of convalescent diphtheria. Fromm[18] found the blood pressure elevated in 14 per cent of his 1,290 cases. Of these, only three showed a residual hypertension when re-examined at a period of from six months to four years later. Albumin and casts appeared in a few cases, but rarely red blood cells, and there was no apparent correlation between the blood pressure and the urinary findings.

Reports of hypertension in postdiphtheritic paralysis are even more rare than its occurrence in the acute diphtheritic infection. Rolleston,[9] Kollosowa,[14] and Friedemann[2] found lowering of the blood pressure in early progressive paralysis and considered this of prognostic value. Fiedler[10] reported two cases of postdiphtheritic paralysis in which the blood pressure was low at the time of onset of paralysis, increased as the paralysis progressed, and was at its height during the height of paralysis. One case, reported in detail, was that of a 2½-year-old girl with proved tonsillar diphtheria. Her urine showed albumin, white blood cells, and hyaline and granular casts on admission; the albumin and hyaline casts persisted for about three weeks. Blood pressure on admission was 60 to 65 mm. systolic, and varied from 60 to 70 for the first two weeks. Two weeks after onset, paralysis of the uvula appeared, and her blood pressure began to climb gradually. One week later, she had ataxia of the lower extremities and absent patellar reflexes. At this time, the blood pressure was 105, and it varied between 105 and 122 during the next three and one-half weeks (fifth through eighth weeks of illness). Paralysis of the abducens appeared during this period of hypertension. During the ninth and tenth weeks, the blood pressure was constant between 100 and 105, and the abducens and uvular paralyses gradually disappeared. At the time of discharge from the hospital, slight ataxia remained.

Von Kiss[15] reported elevation of blood pressure in four of the six fatal cases of postdiphtheritic paralysis that he studied. All of the patients had clinical and electrocardiographic signs of severe cardiac damage, and they died with symptoms of cardiac failure. Autopsy was performed in all cases, and degeneration of cardiac muscle was demonstrated. Brief abstracts of the four cases with elevated pressure follow:

CASE 1.—A 10-year-old boy who developed paralysis of the legs, paresis of the hands, and dysphonia five weeks after a severe attack of pharyngeal diphtheria, died on the tenth day of hospitalization. The blood pressure ranged from 115/65 to 135/115. The last-mentioned value occurred one and one-half hours before death.

CASE 2.—A 4-year-old boy was admitted in the sixth week of his diphtheria with postdiphtheritic paralysis. During his seven days of hospitalization, his blood pressure was somewhat higher than normal for his age, ranging from 100/70 to 115/85. On the day of death repeated readings ranged from 100/75 to 110/75. The latter measurement was taken only ten minutes before death.

CASE 3.—A 2¾-year-old boy developed severe postdiphtheritic paralysis on the forty-eighth day of his diphtheria. On the day of death, his blood pressure was 100/60 to 100/55 until two hours before expiration. The last measurement, taken twenty-seven minutes before death, was 86/55.

CASE 4.—A 9-year-old girl with severe postdiphtheritic paralysis and cardiac failure on the fifty-second day of diphtheria. Died on the day of admission to the hospital. The blood pressure ranged from 100/75 to 125/95; five minutes before death, her blood pressure was 110/100.

Lutz[17] mentions two cases of postdiphtheritic paralysis with recovery. One was that of a 14-year-old boy whose blood pressure during the first two weeks of paralysis varied "between high and low values," with a slow rise to 125 mm. At time of discharge from the hospital, systolic pressure was 110 mm.

Ever since blood pressure changes in diphtheria were first noted, there has been much speculation concerning the etiology of such variations. Romberg, Passler, Bruhns, and Muller (1899) drew the conclusion from their animal experiments that, in the acute phase of diphtheria, the cause of death lay in paralysis of the vasomotor center in the medulla, with consequent fall in blood pressure. They claimed that vasomotor paralysis, not myocardial weakness, was the chief cause of circulatory failure. According to this concept, hypotension is due to toxic injury to the vasomotor center, and hypertension is caused by its stimulation. Deprivation of oxygen, such as occurs in air-hunger and laryngeal obstruction, would cause a temporary anemia of the center, with a response of peripheral vasoconstriction due to the outpouring of adrenalin by the splanchnic nerve reflex.

Hyperemia of the brain with hemorrhage and high-grade cerebral edema is often seen in autopsy sections. The explanation of hypertension in such children through increased cerebral pressure and consequent marked compression of the medullary centers would be completely understandable. This is supported by the experiments of Friedemann, who found increased spinal fluid pressure without increased protein or cells as a constant symptom in severe diphtheria.

The histologic investigations of Von Kiss and Horanyi[20] contradict the theory of vasomotor center injury. They were unable to demonstrate anatomic changes in the vasomotor centers, either in children dead from diphtheria or in animals poisoned by diphtheria toxin. They felt that the vegetative nervous system in human beings, guinea pigs, and horses did not seem to have affinity for diphtheria toxin.

Many attempts have been made to correlate the pathologic urinary findings found in some cases of diphtheria with changes in blood pressure. However, the reaction of the kidneys to the diphtheria toxin is with an epithelial nephrosis, not a glomerular nephritis, and there is rarely hematuria or increased nonprotein nitrogen. Bartel[21] found erythrocytes in the sediment in only ninety-three isolated urinalyses of

the 1,290 cases he investigated, and only six of these cases had elevation of blood pressure. As stated above, Fromm found no correlation between the hypertension he observed in 182 diphtheritic children and their urinary findings. Lutz and Fromm attribute the hypertension occasionally found in diphtheria to toxic damage to the adrenals. The adrenals have been shown to present degenerative stigmas in experimental diphtheria poisoning, and observers[22, 23] have claimed that diphtheria toxin has an affinity for adrenal chromaffin tissue. Fromm felt that the degree of vascular contraction, and, therefore, of the hypertension, is dependent upon the individual susceptibility to the adrenal hormone, i.e., the vasolability.

In considering the cases of hypertension associated with postdiphtheritic paralysis, a neurologic etiology would seem most tenable. Salus[24] reported three cases of paralysis with hypertension which are of sufficient interest in this connection to summarize briefly.

CASE 1.—A 21-year-old man with bulbar poliomyelitis of two days' duration who died of respiratory paralysis six hours after admission. His systolic blood pressure was 190 to 200.

CASE 2.—A 30-year-old male with an ascending myelitis and flaccid tetraplegia. As the paralysis approached the upper extremities and recurrent laryngeal paralysis occurred, his blood pressure rose steadily from 110/70 to 190/90. With improvement of the paralysis, the blood pressure sank, and six months after the onset of illness it reached normal and remained so. Urinalysis, nonprotein nitrogen and renal concentration tests were normal.

CASE 3.—A 46-year-old woman with ascending myelitis and flaccid tetraplegia. Her tongue was protruded to the right, and she had dysphagia and dysphonia. Her systolic blood pressure fluctuated from 180 to 130 from day to day. The paralysis gradually cleared, and, concomitantly, the blood pressure slowly dropped to 90/50 and became stable. There was no evidence of renal disease. Both of Salus' surviving cases showed marked instability of the blood pressure and pulse rate, and one exhibited extreme slowing of the heart in response to vagal pressure during the acute phase of his illness and a normal response after he was well.

In the two patients who survived, the hypertension, marked lability of pressure, tachycardia, and increased respirations all came on with the ascending paralysis at the time that bulbar symptoms appeared, and they gradually cleared as the paralysis improved.

Muller and Nordmann[25] report a similar case in which the blood pressure reached 209/140. They found a lesion in the substantia reticularis grisea to which they attributed the hypertension. These cases of paralysis with hypertension bear a striking resemblance to the cases of postdiphtheritic paralysis reported in this paper. In all of them, the symptoms of hypertension came on at the same time as the paralysis, and gradually cleared as the paralysis improved. Fishberg[26] states that "inasmuch as lesions of the type encountered in poliomyelitis cause destruction with loss of function of the part of the nervous system involved, the hypertension in these cases must be attributed either to damage to

a vasodilator center or else to injury to fibers or a center which serve to inhibit the vasoconstrictor centers.'' Since all of these cases showed either hypoglossal or vagal paralysis, the hypertension might be due to irritation of the neighboring glossopharyngeal nerve, such as one sees in glossopharyngeal neuralgia. This reflex is mediated through the carotid sinus.

SUMMARY

Two cases of postdiphtheritic paralysis accompanied by hypertension are reported. The blood pressure increased as the paralysis progressed and gradually decreased as the paralysis cleared. Several comparable cases were cited from the literature. Review of the literature reveals that the occurrence of hypertension in children is not uncommon.

Various etiological possibilities were mentioned. It seems most likely that late hypertension coming on at the time of paralysis is of neurologic origin, attributed either to damage to a center in the medulla or mediated by irritation of nerve fibers similar to the carotid sinus reflex.

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DIPHTHERIA TREATED WITH SULFANILAMIDE

Report of a Case

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SINCE the use of sulfanilamide in the therapy of hemolytic streptococcic infections was begun in this country in 1937, the drug has been found effective against diseases of other bacteriologic etiology as well. It is likely that continued experimental and clinical investigation with sulfanilamide and its derivatives will open new fields for its application as time goes by.

Faulkner,[1] in 1939, reported four cases of diphtheria; one of these patients received sulfanilamide alone in treatment, with complete recovery. In concluding he stated that "one wonders if the sulfanilamide had any effect on the *Corynebacterium diphtheriae*." To date, I have been unable to find in the literature any similar case, and, as a result, I am reporting a case of diphtheria in which the use of sulfanilamide alone resulted in clinical and bacteriologic control of the infection. It is hoped that this report may stimulate more thorough investigation along this line in localities where diphtheria is more prevalent and where the facilities for such investigations are of the best.

C. B., a 10-year-old girl, was seen at her home at 6 o'clock on the evening of Feb. 6, 1940. The mother had previously stated over the telephone that the child had a severe sore throat which had been observed for the first time the day before. Exactly three months ago the child had been ill with scarlet fever and had made an uneventful recovery. At that time cultures of her throat produced numerous hemolytic streptococci, and she was subsequently released from isolation by the State Health Department after several throat cultures were found negative for any pathogenic microorganisms.

The child when first seen during the present illness was acutely ill, and the temperature was 102° F. by mouth. Physical examination was entirely negative, with the exception of a markedly injected nasopharynx and large swollen tonsils covered by a thick grayish membrane. A nose and throat culture was taken and a direct smear made before any treatment was instituted. The direct smear was examined by the Health Department technician at 8 P.M. the same evening. He reported it "negative for diphtheria," and the culture was placed in the incubator for further observation. While awaiting the report of the culture, and since the smear had disclosed some streptococci, sulfanilamide was begun in the usual calculated dosage so as not to lose time should the membrane be merely a pseudomembrane concomitant with a streptococcus infection.

At 8 o'clock the following morning the Health Department reported that the culture showed a heavy growth of diphtheria bacilli, and antitoxin was taken to the home of the patient to be administered immediately.

On arrival the child was found sitting in bed and apparently feeling well. All evidence of acute illness had subsided, and, when questioned concerning her throat,

she stated that the soreness had practically disappeared. Physical examination revealed no fever and almost complete absence of the membrane noticed the night before. The swelling and injection of the tonsils had subsided markedly. In view of this marked improvement, no antitoxin was given. Another throat and nose culture was obtained, after which the throat was swabbed with 10 per cent aqueous mercurochrome. The child was kept on a liquid diet with other supportive measures, and the administration of the sulfanilamide was continued.

At no time after the first twenty-four hours did the child have a temperature above 98.6° F. Her diet was rapidly changed to soft food, followed in several days by her usual diet. For two days routine swabbing of the throat with 10 per cent mercurochrome was performed and then discontinued, the child being asked to use a throat gargle of hexylresorcinol (S.T. 37) at intervals. Throat cultures taken on February 7, 8, 10, 12, and 16 were all positive for diphtheria, the nose cultures being negative throughout. On Feb. 21, 1940, negative throat and nose cultures were obtained, and the child was released from isolation by the Health Department. The sulfanilamide had been reduced in dosage during this time and finally had been discontinued on Feb. 17, 1940.

COMMENT

One might be tempted to say that this child was merely a diphtheria carrier who developed an acute throat infection with pseudomembrane formation, but opposing this assumption are the negative throat cultures obtained following the scarlet fever infection in November, 1939, and the scarcity of other pathogenic bacteria found in the throat at the present time. At least, under ordinary circumstances this child would have been treated with antitoxin in view of the positive cultures and the presence of a typical membrane.

I regret the fact that a virulence test was not performed, although it was ordered. However, all other cases of diphtheria in this locality existing at the time of the described case were definitely virulent.

CONCLUSION

A case of diphtheria has been described in which complete control of the symptoms following the use of sulfanilamide is shown.

It remains to be seen whether further clinical experience will substantiate the practical value of chemotherapeutic treatment in carefully selected cases of uncomplicated diphtheria.

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THE TREATMENT OF MENINGITIS DUE TO HEMOPHILUS INFLUENZAE (PFEIFFER'S BACILLUS)

A Review of 108 Cases

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MENINGITIS due to *Hemophilus influenzae* or Pfeiffer's bacillus is rarely seen in the adult patient, but is one of the most common of the meningitides in children. Table I shows the frequency of its occurrence in a series of 642 cases at the Children's Hospital, Washington, D. C. Excluding tuberculous meningitis, it is the most common form of meningitis in a child under 2 years of age.

Table I

Types of Meningitis

(642 cases: jan. 1, 1924, to march 31, 1939)

	Number of Cases	Percentage
Tuberculous	205	31.9
Meningococcic	180	28.0
Influenzal (*H. influenzae*)	100	15.6
Pneumococcic	73	11.4
Streptococcic	50	7.8
Staphylococcic	5	0.8
Friedländer's bacillus	1	1.6
Morgan's bacillus	1	1.6
Undetermined	27	4.2

Age, Sex and Race

The average age in this series of 108 patients is 2.14 years. The relation of age to recovery is given in Table II, and in Table III there is evidence that males are more likely to be affected than females, a finding we have noted for all types of meningitis, with the exception of that due to the meningococcus. On study of the ratio of the number of admissions of white and colored patients (2:1), we find that both races are equally susceptible.

Table II

Relation of Age to Recovery: 108 Cases

No Serum		Serum; No Complement		Serum and Complement	
Recovered	Died	Recovered	Died	Recovered	Died
2	69	0	6	9	22
Average age in years:					
4.00	1.725	0.00	1.47	3.72	2.48

Average age for all cases, 2.14 years.

Read at the Meeting of Region I of the American Academy of Pediatrics, Washington, D. C., April 5, 1940.

From the Medical and Laboratory Services, Children's Hospital, Washington, D. C.

TABLE III

RELATION OF SEX AND RACE: 108 CASES

SEX		RACE	
MALE	FEMALE	WHITE	COLORED
63	45	72	36

SEASONAL INCIDENCE

The prevalence of *H. influenzae* meningitis roughly coincides with the incidence of respiratory disease as shown in Fig. 1.

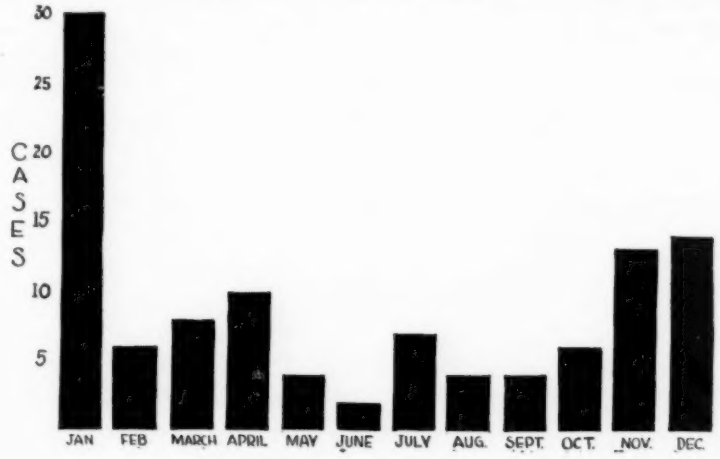

Fig. 1.—Seasonal incidence.

PREDISPOSING CAUSES

This disease is usually termed a primary disease. There are certain factors operating to render these patients susceptible to meningeal invasion by *H. influenzae*. The age of the child has much to do with this. At the period of maximum susceptibility, maternal immunity has been nearly dissipated and there has been insufficient time for acquiring

TABLE IV

ILLNESSES WHICH PRECEDED *H. influenzae* MENINGITIS

	CASES
Rhinopharyngitis	21
Pneumonia	20
Otitis media	18
Florid rickets	4
Pertussis	2
Mumps	2
Bronchitis	2
Osteomyelitis	2
Lung abscess	1
Pericarditis	1

natural immunity. The fact that those who recovered were nearly twice as old as those dying would indicate this. Most of these patients were quite anemic on admission, and the majority came from families in the lower income group. These facts suggest the lack of proper food, vitamins, and care. Table IV reveals the influence of other factors in relation to this disease.

INITIAL SYMPTOMS AND PHYSICAL SIGNS

Lack of leading symptoms and signs because of the age of these patients makes diagnosis rather difficult and often delayed. The commoner symptoms and signs are given in Table V.

TABLE V

COMMON INITIAL SYMPTOMS AND PHYSICAL SIGNS

	CASES
Vomiting	46
Stiff neck	39
Increased or absent reflexes	20
Irritability	19
Cough	17
Convulsions	12
Semicoma	10
Positive Kernig's sign	9
Headache	5
Coma	2

LABORATORY FINDINGS

The increase in the number of cases of *H. influenzae* meningitis reported is probably due to improved methods of bacteriologic diagnosis rather than to an actual increase in the disease. Pfeiffer's bacillus exhibits greater pleomorphism than any other microorganism responsible for meningeal infections. When seen early in the disease, the organisms may be very scarce and are usually short and often coccoid in appearance. Short chains are sometimes noted, and capsule formation is not infrequently observed when stained by Gram's method. Later in the disease, long filamentous forms may appear, and, if death ensues, they are usually numerous by that time. With few exceptions, *H. influenzae* isolated from the spinal fluid in this series belonged to Type b, there being an occasional member of Types a and f.

The ring or precipitation test has aided us in making a diagnosis as to the type of meningitis. Anti-*H. influenzae* serum is overlaid with the supernatant centrifuged spinal fluid. A grayish-white ring appearing at the point of contact after ten minutes is diagnostic; however, a negative reaction does not preclude the possibility of an infection due to this organism.

The leucocyte count of the blood averages 18,000, but may be as high as 35,000 or as low as 5,000. A low leucocyte count in meningitis should

make one suspicious of either tuberculous or *H. influenzae* meningitis; however, one should remember that fulminating meningococcic meningitis will also give a leucopenia.

PATHOLOGY

The usual findings are well known and do not need recounting here; however, it may be well to note some changes which are incident to the prolongation of life due to improved treatment. Formerly, without specific serum therapy, the patient lived approximately nine days. With intraspinal serum-complement treatment the duration of the disease in a patient who succumbs is from twenty-one to thirty days, long enough to allow organization of the exudate at the base of the brain, with resultant obstruction of the flow of fluid from the ventricles to the spinal meninges. Internal hydrocephalus or pyocephalus, as a result, has increased in frequency. Two patients who died in less than twenty-four hours had purpura with adrenal hemorrhage, the typical Waterhouse-Friderichsen syndrome, usually attributed to the meningococcus as the etiological agent.

TREATMENT

The increased effectiveness of our present specific treatment is due in part to the work of Pittman,[1, 2] who demonstrated that the strains of *H. influenzae* isolated from the meninges of meningitis patients usually belong to one group designated by her[3] as Type b, a few strains falling into Types a and f. These meningeal strains are smooth and encapsulated in comparison to the respiratory strains which are rough and serologically fall into a rather heterogenous group which are not encapsulated. Ward and Wright,[4] Wright and Ward,[5] Ward and Fothergill,[6] and Fothergill[7] have verified Pittman's observations. By using virulent meningeal strains of *H. influenzae*, potent antisera have been produced and are available for clinical use.

Lack of benefit from serum therapy in the past would seem to be due to two factors, viz., lack of potent bactericidal serum and failure to use complement intrathecally for the activation of the serum. Ward and Wright[4] expressed the need for the combination of a specific bactericidal serum and complement in the intraspinal treatment of those with meningitis due to *H. influenzae*. The work of Fothergill[7-9] has been outstanding in showing the necessity for this combination of antiserum and complement.

In 1935 we[10] reported fifty-eight cases of meningitis due to the Pfeiffer bacillus, and of these, but one lived. Wilkes-Weiss and Huntington,[11] in 1936, after reviewing the literature, reported 500 patients of all ages with *H. influenzae* meningitis, with thirty-five recoveries, a mortality percentage of 92.2. Ten of the 500 patients received serum therapy, with one recovery. Their statistics and others published in-

dicated a recovery of between 1 and 2 per cent in children who did not receive antiserum-complement intraspinally.

Since 1935, practically all patients at this hospital with this type of meningitis have received the anti-influenza bacillus serum prepared by the Massachusetts Department of Public Health.* During 1935 and 1936, six received the antiserum without complement, in addition to spinal drainage and transfusions; none survived. Of thirty-one receiving serum-complement intraspinally, nine lived, 29.1 per cent recovering. The serum-complement mixture has been used in practically all cases at the Children's Hospital in Washington, D. C., since 1937, according to the plan developed by Fothergill.[7-9]†

The source of the complement used in the treatment of most of the earlier patients was the guinea pig, human complement being used more recently. The work of Dingle, Fothergill, and Chandler[12] would indicate that complement from this animal will not activate the bactericidal antibodies in anti-*H. influenzae* serum from the horse. For this reason, guinea pig complement has not been used here routinely during 1938 and 1939, although the results obtained in 1937 were excellent, four of ten patients surviving. This gives the impression that in vivo the antiserum from the horse and guinea pig complement may not be without some beneficial effect.

After the diagnosis has been established and as much cerebrospinal fluid has been drained off as possible, the patient receives between 10 and 20 c.c. of a 2:1 mixture of anti-*H. influenzae* serum-complement. In order not to delay treatment, lyophilized guinea pig serum (complement), because of its immediate availability, has been used frequently for the first intrathecal treatment. Donors are bled for further complement. Recently the blood bank has maintained a supply of human complement for immediate use. From 30 to 60 c.c. of specific antiserum is given intravenously in physiologic salt solution, the same dose being given intravenously or intramuscularly the following day. Intramuscular injections of serum in amounts of from 10 to 30 c.c. have been given in some cases for four consecutive days. Transfusion of citrated blood is also given and repeated as indicated during the course of the illness because of the usual anemic state of these patients and their lowered resistance. Sulfanilamide, and more recently sulfapyridine, are administered as soon as possible, the former orally or subcutaneously, and the latter orally with the sodium salt intravenously. More recently, the serum-complement mixture has been given intrathecally with an equal quantity of 2 per cent solution of sodium sulfapyridine, as suggested by Neal.[13] The dose sufficient to give a spinal fluid concentration of 10 mg. per cent is thought to be sufficient. Cevitamic acid

*This serum was supplied by Dr. LeRoy D. Fothergill, Harvard Medical School, Boston.

†Sharp and Dohme, Philadelphia, Pa., supplied the lyophilized guinea pig and human serum (complement). All of the recovered patients who received guinea pig complement and one patient treated with human complement received lyophilized serum prepared by this company.

in amounts of between 150 and 300 mg. daily is prescribed. An adequate fluid and carbohydrate intake is given orally or parenterally. Hartmann's solution has been frequently used. The intraspinal treatment is continued daily until the spinal fluid remains sterile for at least two days. For the relief of increased intracranial pressure, additional spinal taps are done as indicated. Evidence of cerebrospinal block has been noted in a number of patients; combined cisternal and spinal punctures were done to establish this diagnosis.

Sometimes the introduction of serum or physiologic salt solution through the lower needle will be sufficient to relieve the obstruction; in other cases, air has been introduced under pressure through the spinal needle with breaking up of the block. This procedure is not without danger from respiratory death. Cisternal puncture, although necessary at times, becomes increasingly hazardous in proportion to the amount of fibrinous exudate deposited in the region of the foramen magnum.

In two patients whose clinical state had become unsatisfactory, two different procedures were instituted, with subsequent improvement and eventual recovery of the patients. In one case, McLendon and Mitchell[14] gave typhoid vaccine intravenously for its nonspecific protein effect, with apparent benefit; in another, Rafetto[15] gave three intravenous injections of 100 mg. cevitamic acid on the thirty-sixth, fortieth, and forty-fifth days of illness. Due to feeding difficulties, this patient was probably in a state of avitaminosis.

TABLE VI

ANALYSIS OF RESULTS OF TREATMENT. INADEQUATE THERAPY

TREATMENT	NUMBER OF CASES	LIVED	DIED	PERCENTAGE OF MORTALITY
No serum	71	2	69	97.18
Anti-*H. influenzae* serum; no complement	6	0	6	100.00
Total	77	2	75	97.40

TABLE VII

ANALYSIS OF TREATMENT WITH ANTI-*H. influenzae* SERUM-COMPLEMENT. NO CHEMOTHERAPY

SPECIFIC SERUM WITH	NUMBER OF CASES	RECOVERED	DIED	PERCENTAGE OF MORTALITY
Guinea pig complement	16	3	13	81.25
Human complement	2	0	2	100.00
Total	18	3	15	83.33

We believe that the rationale of much of the present plan of treatment has been justified by the results shown in Tables VI, VII, and VIII, and by the reports from others who have had considerable experience in treating this disease. Fothergill's[9] report (Table IX) and

TABLE VIII

ANALYSIS OF TREATMENT WITH ANTI-*H. influenzae* SERUM-COMPLEMENT, SULFANILAMIDE AND SULFAPYRIDINE

SPECIFIC SERUM WITH	NUMBER OF CASES	RECOVERED	DIED	PERCENTAGE OF MORTALITY
Guinea pig complement Sulfanilamide	2	1	1	50.00
Human complement Sulfanilamide Sulfapyridine	3	1	2	66.66
Human complement Sulfanilamide	5	2	3	60.00
Human complement Sulfapyridine	3	2	1	33.33
Total	13	6	7	53.85

TABLE IX

RESULTS OF IMPROVED TREATMENT OF MENINGITIS DUE TO *H. influenzae*

REPORTED BY	TOTAL CASES	RECOVERED	MORTALITY PERCENTAGE
Fothergill[9]	201	31	84.6
Silverthorne[16] (Toronto)			
1919-29	70	1	98.6
1930-39	65	15	76.9
Hodes[20] (Baltimore)			
Mass. Dept. Public Health Serum	16	3	81.3
Commercial Serum	10	0	100.0
Sulfapyridine; no serum	4	1	75.0
Eldahl[21]			
Sulfanilamide; no serum	3	2	33.3
Neal[13] (New York)			
Sulfapyridine and sulfanilamide, with and without specific serum	29	14	48.3
Lindsay, Rice, and Selinger			
Inadequate treatment	77	2	97.4
Specific serum and complement	18	3	83.3
Specific serum, complement, sulfanilamide and/or sulfapyridine	13	6	53.8

the experience of Silverthorne[16] and the physicians of Children's Hospital leave no doubt as to its value. Sulfanilamide and sulfapyridine appear to be of definite help in the treatment of this disease, as indicated by Tables VIII and IX. The splendid results obtained by Neal[13] in a large series of patients would seem to establish the value of chemotherapy in the treatment of this disease. The work of Povitsky[17] and Pittman,[18] together with reports by Hamilton and Neff,[19] Hodes,[20] Eldahl,[21] and Netter,[22] would also tend to coincide with our clinical impression.

There has been considerable argument concerning the value of cevitamic acid in infections. The fact that most of these meningitis patients are from families of the lower income group would indicate its use in adequate amounts. Certainly it can do no harm.

The value of transfusions and parenteral fluids is obvious. Their use prior to the giving of serum-complement was of definite value, and their worth at present is unquestioned. The patients who recovered received an average of 5.6 transfusions, 5.4 intravenous and 9.3 subcutaneous injections.

Of equal importance is the medical and nursing staff of a hospital. The medical staff should be well trained in the diagnosis and treatment of meningitis, and the necessary therapeutic agents and apparatus should be available for immediate use.

SUMMARY

Meningitis due to *H. influenzae* is relatively common in children. Excluding tuberculous meningitis, it is the commonest cause of meningitis in children under 2 years of age. The average age in this series of 108 patients was 2.14 years.

The treatment of this type of meningitis with specific serum and human complement intrathecally, intravenous serum, with adequate supportive treatment consisting of transfusions, fluids, and vitamins, has reduced the mortality percentage from 97 to 83. By adding sulfanilamide and sulfapyridine to the above, the mortality for thirteen cases has been further reduced to 54 per cent.

Grateful acknowledgment is made to Dr. Leroy D. Fothergill, Harvard Medical School, Boston, Mass., and to Dr. Margaret Pittman and Dr. Sara Branham, National Institute of Health, Washington, D. C., for valuable aid and advice in the treatment of these patients; and also to Dr. William A. Feirer, Sharp and Dohme, Philadelphia, Pa., who arranged for the supply of lyophilized serum (complement).

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INFLUENZAL MENINGITIS

Case Report

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PRIOR to the use of chemotherapy, case reports of recovery from *Hemophilus influenzae* meningitis appeared in the literature spo-

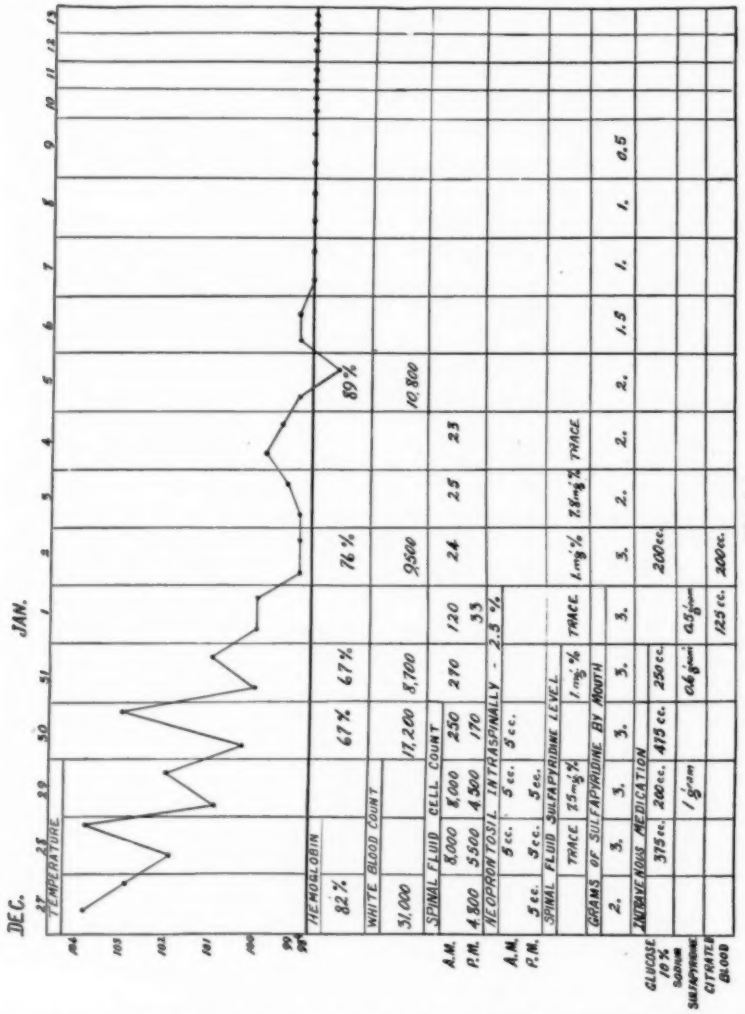

Chart 1.

radically.[1] Since the introduction of sulfanilamide, case reports of recovery have become increasingly frequent.[2] Until the present time, only

five cases of recovery following the use of sulfapyridine have been reported in the English literature.[3] The following case presented no unusual findings other than recovery and is reported to stimulate interest in recording cases of cure.

CASE REPORT

A white girl, 27 months of age, was admitted to the Pediatric Service of Watts Hospital, Durham, N. C., on Dec. 27, 1939, at noon, with a diagnosis of meningitis. A history was obtained that the infant had had a slight cold of one week's duration, but had been well otherwise. On the previous day at 2:00 P.M., after eating a hearty luncheon, just as she was leaving the table she fell and bumped her head on the floor. She cried a little at the time, and then went to sleep. The child remained drowsy and was hard to arouse, so the parents took her to the local physician. No diagnosis was made, but intracranial injury was suspected. The parents were told to take the child home and to hold her in their arms in order to watch her closely. This was done. The child vomited once during the night. Early in the morning of admission she was more drowsy and was taken to the office of the referring physician. The family and personal histories were irrelevant.

Physical Examination on Admission.—The temperature was 103.8° F. rectally; pulse, 130; respirations, 30. The patient was a well-nourished, acutely ill, semistuporous girl. The skin was dry and hot, with numerous impetiginous lesions on the body. The face was flushed, the lips were chapped, sordes of the teeth and gums were present, and the tongue was coated. Both eardrums were injected. The anterior chain of lymph nodes was enlarged. The pupils were small and regular, but sluggish. The neck was rather stiff, with some evidence of pain on flexion. The spine was slightly rigid. Kernig, Brudzinski, and Babinski signs were all absent. X-ray examination of the skull revealed no evidence of fracture.

Course.—An immediate spinal puncture was done, revealing 4,800 cells, mostly polymorphonuclear, with many gram-negative rods and diplococcoid forms in the direct smear. *Hemophilus influenzae* was obtained on culture. As shown in Chart 1, the child was given 1 Gm. (gr. xv) sulfapyridine by mouth, followed by 0.5 Gm. (gr. viiss) every four hours. Lumbar drainage, with instillation of neoprontosil (2.5 per cent) solution, was done twice daily for the first four days. Sodium sulfapyridine was given intravenously if the child vomited the oral dose. The child gradually responded to treatment, and the temperature fell to 99° F. on the sixth day, to normal on the tenth day, and remained so until discharge on the seventeenth hospital day. There were no residual neurologic signs at that time, nor when the child was examined one month later.

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TEN "GOOD" EATERS AND TEN "POOR" EATERS

Developmental Background and Behavior Relevant to Nutrition and Health of a Group of Nursery School Children

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LACK of appetite and poor eating behavior among young children are still common problems presented to pediatricians and nutritionists, although experiments in the self-selection of diets, pioneered by Davis,[1] and the policy of lessened adult pressure, advocated by such workers as Aldrich,[2] Brennemann,[3] and Gesell and Ilg,[4] have helped toward emancipating children at the dinner table. Valuable as these contributions are, however, further illumination is needed in order to deal adequately with certain feeding problems.

A group of sixty-six children, enrolled in the junior nursery school of the New York State College of Home Economics, during the five years, 1932-37, was studied as to various kinds of behavior relevant to nutrition and health.[5] In this investigation, daily observations throughout each school year, made by the staff and the parents, covered nearly all routine phases of the children's lives. Hours of sleep for nap and night, length of time required to fall asleep, and time of getting up in the morning were recorded; bowel movements and enuresis; hours of outdoor play; amounts eaten at the nursery school noon meal and time required for eating; food preferences as indicated by amounts of second servings and order of eating; the number of types of nervous behavior shown during each five minutes of the noon meal; weekly weighings and monthly measurements of height; onset and duration of illnesses were among the many facts recorded for these children.

The method of analysis comprised coding this information into numbers which were then punched into cards and sorted on Hollerith machines. Thus, each card represented the happenings of one day in the life of a nursery school child. Over 13,000 of these cards, describing 13,000 days, averaging about 200 days per child, were included in the analysis.

The first step was to determine the norms for this group of sixty-six healthy children, representative of parents from the professions, good homes, and favorable environments.[5a] With norms established, variations were studied, such as differences in the behavior of the sexes; variations in the behavior of the entire group during the different school months

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and seasons; differences in the behavior of the ten children most overweight and the ten most underweight for height. These results will be reported elsewhere.

In a detailed study of the learning of ten "good" eaters and ten "poor" eaters selected from the large group,[6] it was observed that there were considerable variations both in physique and development, as well as in behavior. These are reported here in the hope of aiding in a better understanding of the underlying causes of lack of appetite and some of the behavior associated with it.

These twenty children were selected from three different years during the larger investigation when series of menus were repeated over and over in order to study their learning to like new and disliked foods and combinations of foods. Their selection was based upon their eating efficiency the first month of school. A method of describing a child's eating efficiency has been in use in the Cornell Nursery School for the past eight years and has been described by the staff in a symposium on nursery school feeding practices.[7] The food consumed is estimated in arbitrary units, approximately equivalent to twenty calories each. The time taken to eat the meal is recorded in minutes. A simple formula is then used to denote the relationship between the amount of food eaten and the time taken to eat it. From the number 100 is subtracted the number of minutes required for the meal; to this is added the number of units eaten, which yields a score descriptive of the child's eating efficiency at that particular meal. For example, here is a typical meal eaten by a preschool child and his amounts:

MENU	FIRST SERVING	SECOND SERVING	UNITS
Meat loaf	1 tablespoon	3 tablespoons	4
Buttered cabbage	1 tablespoon	½ tablespoon	1½
Mashed potato	1 tablespoon	3 tablespoons	4
Rye crisp	1 piece	7 pieces	8
Milk	½ cup	½ cup	3
Cranberry applesauce	5 tablespoons		5
			25½

If this meal was eaten in forty minutes, the efficiency score would be computed thus:

$$\begin{array}{r} 100 \\ -\ 40 \text{ minutes} \\ \hline 60 \\ +\ 25\tfrac{1}{2} \text{ units} \\ \hline 85\tfrac{1}{2} \text{ efficiency score} \end{array}$$

As the meals are served in the nursery school at Cornell, the amounts most frequently eaten are from 21 to 27 units in from forty to forty-nine minutes, with efficiencies from 71 to 90.

These efficiency scores have given objective measures of children's appetites and eating behavior. The ten "good" eaters were those chil-

dren who had the highest median efficiency the first month of nursery school, and the ten "poor" eaters were those with the lowest. Although these children were selected on the basis of their eating behavior the first month, nevertheless, in general, the one group continued to be superior to the other during the entire course of the school year.

As a further description, when the eating behavior of these two groups is compared to that of all the sixty-six children during the five-year period, the "good" eaters were in the upper percentiles of this larger group, while the "poor" eaters ranked near the bottom.

Although it would not be fair to call all of the "poor" eaters cases of anorexia, they represented the children who, during three years, showed the lowest efficiency, tending to require a long time to eat small amounts. On the other hand, the "good" eaters were those who showed the highest efficiency, tending to eat large amounts promptly.

The chronologic ages of the children in the two groups at the beginning of school were similar, averaging 30.1 months for the "good" eaters and 30.2 months for the "poor" ones. The median for the group of sixty-six children to which these extremes are compared was in the same age range.

In the selected group were twelve boys and eight girls. Among the "good" eaters were five of each sex, but the group of "poor" eaters consisted of seven boys and three girls.

With the number in each group limited, it was possible to include many aspects of development and behavior for intensive study. It is believed that the trends shown by these children, defining the outer boundaries of the larger group, may be suggestive for further investigations.

DEVELOPMENTAL BACKGROUND

When certain factors in the lives of these two groups were compared, some of those which might be related to appetite and eating behavior were not significantly different. But certain other conditions showed distinct variations between the two groups.

Birth and Infancy.—The age of the mothers at the time the children were born was not significantly different for the children of the two groups, averaging 29 years for the "good" eaters and 29.9 for the "poor" ones. There were few complications during pregnancy, and most of the children in each group were full- or nearly full-term babies, with the exception of one "poor" eater who arrived at seven and one-half months.

Birth weights suggest a difference between the two groups in that more "good" eaters arrived as heavier babies. Three of the "good" eaters weighed 9 pounds or over, while none in the other group reached this weight. Since male babies usually weigh more than females and

there were seven males in the group of "poor" eaters and but five in the other group, this difference seems significant.

Early infant histories yielded little variation between the groups. Schedules of feeding and sleeping, breast feeding, milk formulas, appearance of teeth, times of walking and talking, and early health histories all appeared comparable.

On Beginning School: Physical Examinations.—The physical examinations at the beginning of nursery school showed definite differences. The "good" eaters weighed more and also were more above their average weights for heights. They had higher weight-height indices. In height, however, there was little difference between the two groups.

However, when the birth weights were subtracted from the weights on entrance and divided by the number of months of age of the children to determine how rapidly they had gained weight, no difference was apparent between the two groups. More of the "good" eaters at 2½ years were heavier children, although the "poor" eaters had been taking on weight at approximately the same rate.

In tissue tone and muscular development, the two groups differed markedly. Nine of the ten "good" eaters were superior in tissue tone, while eight of the ten "poor" ones were inferior. Muscular development showed nearly the same distribution, with eight of the "good" eaters having superior development and eight of the "poor" ones, inferior.

Many aspects of posture were the same in both groups, but five of the "poor" eaters had winged shoulders, while only one among the others was slightly winged. Six of the "good" eaters had prominent abdomens in contrast to only two of the "poor" eaters who showed moderate distention.

Skin difficulties occurred for the most part among the "good" eaters. Five of them had spots of eczema or patches of roughened skin, while only one of the "poor" eaters had roughness of the eczematous type. The child who showed this was an exception to the group of "poor" eaters in that she was overweight and had superior tissue tone and musculature. Physiologically she seemed to belong to the group of "good" eaters, although her eating behavior at nursery school classed her in the other group.

The only ocular irregularities occurred among the group of "poor" eaters, four of whom had occasional strabismus. When the records for the entire group of sixty-six children were examined, seventeen were found with strabismus. Four of these were the "poor" eaters, which gives a high proportion for a group of ten children.

As for tonsils, among the "good" eaters were two children in whom infection was suggested and two others who had had tonsils removed, in comparison to four among the "poor" eaters with indicated infection and no removals. The incidence was the same, but the treatment differed.

Blood analysis in the fall revealed one "good" eater with hemoglobin below 80 per cent, suggesting slight anemia. But among the "poor" eaters, five had hemoglobin percentages below this reading.

Analyses of urine likewise indicated that the "poor" eaters were at a disadvantage. With the exception of one child with one questionable test on sugar and albumin, the "good" eaters gave negative tests throughout the year. Four of the "poor" eaters, however, gave slight positive tests for sugar occasionally. Albumin was negative. Since, among the sixty-six children, including both the "good" and "poor" eaters, there were only twelve with occasional positive sugar tests, the difference between the groups seems significant.

Mental Development.—It is always of interest to know how children who differ physically compare mentally. Observers have differed in their findings. Some have thought that often children who ate poorly were advanced mentally. There was an indication of an opposite trend in this group of children. Six of the "good" eaters in the fall had I.Q. scores of 115 and better on the Merrill-Palmer tests, while only two of the "poor" eaters did this well.

BEHAVIOR RELEVANT TO NUTRITION AND HEALTH DURING SCHOOL YEAR

Growth.—The school nurse weighed the children weekly without clothing and measured them monthly for height. The rate of growth during school, both in height and weight, was comparable for the two groups. But, because of the initial advantage, the "good" eaters still tended to be the heavier children at the end of the year.

Absences Due to Sickness.—In the attendance record kept by the nurse, under the heading "Colds" were included all types of upper respiratory infections. "Digestive Upsets" included all complaints of the alimentary tract. "Observation" referred to those days when some illness was suspected. Diseases and infections other than colds which occurred among these children were German measles, pyelitis, and conjunctivitis.

Digestive Upsets.—Both in percentage of absence and in actual number of upsets, the "poor" eaters tended to have more digestive difficulty. Only three of the "good" eaters had "upsets," totaling four incidents for the group, while eight of the "poor" eaters had digestive difficulties which kept them at home during the year, a total of twelve episodes for the group.

Colds.—In both percentage of absence and actual number of colds, the "good" eaters tended to have somewhat more colds. Among the ten "good" eaters there were forty-eight colds, and among the ten "poor" eaters there were forty-two colds, lasting in both groups on an average of four days each. This amounted to 83 per cent of the total absences of the "good" eaters caused by colds, in contrast to 69 per cent for the other group.

Other Infections.—Both groups were relatively free of other diseases or infections, and the differences do not seem significant.

In summary, it is interesting to note that the percentage of possible days at nursery school on which the children of the two groups were absent is almost equal, as is the percentage of days absent from school because of illness. The variation was in the causes for absence; the "good" eaters lost a higher proportion of time by colds than the "poor" eaters, while the latter group had a greater proportion of absences because of digestive difficulties. In addition, the "poor" eaters were absent almost twice as often for nonhealth reasons, such as trips, inconvenience to parents, etc.

Eating Behavior.—The variations in eating behavior between the two groups have already been suggested in that the tendency for the "good" eaters throughout the year was to eat the noon meal promptly with high efficiency, in contrast to the "poor" eaters who took an undue time to eat small amounts, giving low efficiency scores.

The study of learning indicated that the "poor" eaters who had most need to learn did show most improvement during the year. But the "poor" eaters were more inconsistent in performance at dinner than the other group, varying more from day to day in amounts eaten and times required for meals. They also tended more often toward a negative kind of learning—the smaller the meal, the longer the time required to consume it. In addition, the "poor" eaters had more barriers to learning when they came to nursery school, in the form of more disliked foods and more foods which were new to them.

The records were examined further to determine if one group was eating more or less of certain types of foods than the other and how they varied from the trends indicated by the sixty-six children. This investigation showed a tendency of the "good" eaters to eat more of each type of food than the "poor" ones, and to eat more of the protein foods, vegetables, potatoes, and desserts than was characteristic of the sixty-six children. The "poor" eaters, on the other hand, tended to eat less of the vegetables, sandwiches, and desserts than the sixty-six children. This may indicate that the "poor" eaters were getting less of the calorie foods and less of the vitamin foods in the meals eaten at nursery school.

Nervous Behavior.—The number of types of nervous behavior shown by each child was noted during each five-minute interval of the nursery school meal. While the tendency was for the "poor" eaters to have more forms of nervous behavior than the other group, both were showing somewhat more than was indicated in the average distribution of all sixty-six children.

Bowel Movements.—Children of both groups ordinarily had one or two bowel movements daily. A tendency is evident, however, for the

TABLE I

SUMMARY OF VARIATIONS BETWEEN TWO GROUPS OF CHILDREN IN DEVELOPMENT AND BEHAVIOR RELEVANT TO NUTRITION AND HEALTH

	TEN "GOOD" EATERS	TEN "POOR" EATERS
Infant History		
Average age of mothers at birth of child (years)	29	29.9
Average birth weights (pounds, ounces)	8-3	7-2
Average number months breast feeding	2.3	2.2
Physical Examination		
Average age, beginning school (months)	30.1	30.2
Average weight, beginning school (pounds)	32.6	30.3
Average height, beginning school (inches)	36.9	36.2
Average monthly gain in weight since birth (pounds)	0.798	0.758
Number superior in tissue tone	9	2
Number superior in musculature	8	2
Number with winged shoulders	1	5
Number with prominent abdomens	6	2
Number with skin suggesting eczema	5	1
Number revealing strabismus	0	4
Number suggesting infected tonsils	4 (2 removed)	4
Number with hemoglobin below 80 per cent	1	5
Number giving positive test for sugar in urine	1	4
Number with I.Q. (Merrill-Palmer) 115 and above	6	2
Behavior During School Year		
Average weekly gain in weight (ounces)	1.79	1.84
Average monthly gain in height (inches)	0.25	0.25
Mean deviations from average weekly weight gains (ounces)	3.17	3.04
Average percentage increment of weight, per four weeks	1.37	1.53
Percentage school days absent, all reasons	18	19
Percentage school days absent, sickness	15	16
Percentage absence due to colds	83	69
Percentage absence due to digestive difficulties	2	12
Percentage absence due to other infections	1	6
Percentage absence due to nonhealth reasons	3	5
Average efficiency eating at school and standard deviation	89 ± 10	74 ± 11.5
Average time for meal and standard deviation (minutes)	40 ± 9.6	51 ± 10.3
Average amount and standard deviation (units)	28.5 ± 5.9	24 ± 6.2
Average number per child of fifty foods never experienced	7	11
Average number per child of fifty foods disliked	1	3.3
Average percentage of meals more than usual amount of nervous behavior was shown.	40	49
Average percentage of days with one bowel movement	66	54
Average percentage of days with two and more bowel movements	33	43
Average percentage of days with no bowel movements	1	3
Average percentage of days dry at night	72	78
Average percentage of days wet at night	28	22

TABLE I—CONT'D

	TEN "GOOD" EATERS	TEN "POOR" EATERS
Average percentage of days with no outdoor play	4	3
Average percentage of days with up to three hours of outdoor play	66	74
Average percentage of days with three hours and more of outdoor play	30	23
Average percentage of days with 13½ and more hours of sleep (nap plus night)	25	31
Average percentage of nights with 12 and more hours of sleep	31	44
Average percentage of days with no nap	9	13
Average percentage of days with naps over 1½ hours	45	31
Average percentage of days in bed for nap before 12:30 P.M.	51	21
Average percentage of days over twenty minutes required to fall asleep	33	46

"poor" eaters to have more days with two movements than the "good" eaters or than the total sixty-six children.

Enuresis.—The tendency toward bed-wetting at nap and at night was rather similar for the two groups. The slight difference, however, was in favor of the "poor" eaters who had more dry nights than the other group.

Outdoor Play.—The "good" eaters had more days with three and more hours of outdoor play than the other group.

Sleeping Behavior.—The amount of sleep obtained during twenty-four hours, including the nap and night sleep, varied slightly for the groups, with a tendency for the "poor" eaters to have more hours. However, the distribution of sleep was different, with shorter naps for the "poor" eaters and more days when no naps were taken. Not only were the "poor" eaters later in starting their afternoon naps, but they took longer to go to sleep. This loss of sleep during the day was made up by earlier times to bed, later rising in the morning, and thus longer night sleep.

All of these differences between the "good" and the "poor" eaters have been summarized in Table I.

The findings reported in this study are comparable with the observations of other investigators. In studies of chronic anorexia, Schultz[8] stressed the body type of the child, stating that "chronic anorexia is seldom, if ever, encountered in the child with rugged physique," but that the subject is commonly "thin, gracile, pale and transparent and usually decidedly underweight. Functionally, he is definitely below par, as is evidenced by the ease with which any dysfunction can be produced and the almost immediate reaction of fatigue to any considerable demand on his physical energy." In addition, "a general lack of muscular tone

of all structures, including the gastrointestinal tract, characterizes these individuals and is directly or indirectly responsible for much of their dysfunction."

Lucas and Pryor,[9] studying 110 children who complained of anorexia, classified their children as linear, lateral, and intermediate and found that 82 per cent of the children complaining of anorexia were linear. "The main complaint of anorexia presented by the 110 children was accompanied by constipation in 46 cases and by indigestion, abdominal pain, or vomiting in 18 cases; 36 suffered from sties, boils, and frequent infections; 62 were underweight, and 41 of these were described as overactive or high-strung, easily fatigued, and irritable."

Of the 349 cases of anorexia analysed by Bartlett,[10] 35 per cent had no discoverable lesions to account for the condition, and he classified these as functional. The commonest pathologic conditions which he found associated with anorexia were septic tonsils and adenoids, acute infectious diseases, tuberculosis, pyelitis, and dental caries.

DISCUSSION AND SUMMARY

Twenty children were selected from a group of sixty-six enrolled in the junior nursery school of the New York State College of Home Economics at Cornell University during 1932-37, on the basis of their eating behavior at the noon meal the first month of nursery school. Ten of these children were "good" eaters with high efficiency who ate promptly. Ten were "poor" eaters who required an undue time, thus eating with low efficiency.

The differences in infant development, physique, and behavior at nursery school have been summarized in Table I and will be discussed here.

Even in a group of healthy, favored children such as make up the enrollment of a university nursery school may be found examples of anorexia and bodily inadequacies such as have been noted by other writers. When the ten selected "poor" eaters were compared to an equal number with superior appetites and eating behavior, it was evident that efficiency in eating was also an indication of their development in other aspects.

The smaller birth weights of the "poor" eaters, the weights still low at nursery school age; the inferior tissue tone and musculature; the tendency toward anemia; the poorer coordination of the eyes; the occasional appearance of sugar in the urine; the lower rating in mental tests; more digestive difficulties during the school year; the tendency toward two bowel movements daily; and more restless activity at mealtime are all suggestive of organisms less far advanced, less stable, and more infantile than the children in the other group.

Therefore, if one believes that the two groups were at different levels of development, marking the extremes for normals, it is not necessary

to infer that one group of children was superior to the other, or that the end products, when growth is completed, will not be so desirable. It is probable that both groups were deviates from the average.

On the other hand, the "good" eaters tended to show more patches of eczema and roughened skin and also more prominent abdomens, as well as more wet beds at night. Possibly these findings are directly related to larger food intakes. More colds among the "good" eaters should be noted, even though in conflict with some of the teachings of nutrition. It seems important to emphasize that slender children of less rugged physique may still be healthy children. Certainly studies of growth in relation to the span of life[11] have taught us to question the virtues of too rapid development.

Similarities in the two groups seem equally as significant as the differences. The age of the mothers at birth; the infant schedules and feeding practices; the arrival of teeth and the beginning of walking and talking were comparable for the two groups, according to the histories. Physical examinations at entrance to nursery school revealed little difference in bony structure and posture, with the exception of more winged shoulders among the "poor" eaters, which might be expected with less fat and perhaps some tendency toward fatigue. While the evidence of infected tonsils was the same, they had been removed from two of the "good" eaters. The amount of absence due to sickness was practically the same, although the reasons varied, with the "good" eaters losing more days because of colds and the "poor" having more digestive difficulties than the other group. The amount of sleep in twenty-four hours was also similar, although the times it was taken varied. The "poor" eaters made up their shorter naps and days without naps by longer night sleep.

Some adults will find heartening the fact that the "poor" eaters as a group tended to gain about equal poundage with the "good" eaters during the school year, although they were unable to catch up with the actual weights of the "good" eaters. In fact, if one considers these equal weights added to smaller bodies, it would suggest more rapid growth on the part of the "poor" eaters. The higher percentage increment per month of the "poor" eaters bears out this impression.

Certain of the findings suggest that there were more differences in the home environments of the two groups than were obvious. In eating behavior, more food dislikes and inexperience with common foods and more time spent over small meals by the "poor" eaters indicate different feeding practices. More days with longer outdoor play for the "good" eaters also point to more favorable home routines, as well as the earlier naptimes and the quick sleep-going at nap. In addition, fewer days kept at home for non-health reasons might imply more regular home schedules.

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THE CHILD'S HISTORY AS AN AID IN THE PSYCHIATRIC TREATMENT OF CHILDREN

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INTRODUCTION

THE following case material illustrates three technical procedures used in the direct psychiatric treatment of neurotic children.

1. Use of the history of the child's life in understanding his present symptoms.

2. Use of the child's dramatic play to understand the problems with which he is attempting to deal through his symptoms.

3. Use of this material to give the child insight into the historical reasons for his feelings and reactions. Through this he becomes better able to distinguish and react to his present real situation instead of dealing with it in the terms of his past experience.

PRESENTING SYMPTOMS

A boy, aged 6½ years, in good physical health, was the middle child of three adopted boys, the oldest of whom was 8½ years, the youngest, 4. The mother adopted children because she had had a bad kidney condition in her adolescence and was told that pregnancy would be fatal. The children knew they were adopted, although the patient apparently did not believe it.

He had many fears—of closed places, of tents, of a canopy over his head, of inflated balloons, of strangers, and of trying anything new. He was afraid of other children. When taken to a party he would begin to cry as soon as he approached the house. When taken inside, he would not speak to anyone or enter into any games, but would stand by himself in a corner. He was much neater than his brothers; in fact, he placed a totally unnecessary insistence on neatness. His appetite was very poor. On a number of occasions, particularly when visiting his maternal grandfather, he would have sudden attacks of vomiting. He was constipated. He twitched in his sleep and had night sweats. He demanded a great deal of attention and had frequent temper tantrums when he did not receive it. This was particularly marked in school. He stuttered at times when he was upset or excited.

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History.—When he was adopted at 4 months of age, he had attacks of diarrhea and vomiting. He had not been breast-fed, showed signs of rickets, and was underweight. Much of his physical care was given to the usual succession of nurses. There was one for the first eighteen months; a second for six months; a third for six months; and then the present one. When the patient was about 1 year old, the parents went abroad for a six-months trip. During their absence the nurse allowed the older child to be severely scalded, but appears to have taken good care of patient. The second nurse preferred the older brother.

He was toilet trained before he was 2 years old. When he was 2½, he was sent to nursery school for one term where he was very dependent and distractible. Physical examination at this time revealed an orthopedic defect. He was placed in braces for one year, and then his knees were operated upon. The operation was followed by casts for several months and then braces day and night. He had a tonsillectomy and adenectomy when he was 3, and at about the same time the mother adopted another baby on whom she lavished much affection. The patient reacted by starting to soil and wet again. The mother, much annoyed by this return of uncleanliness, scolded and punished him for it. A friend of the mother told her that she was not treating the patient fairly, and when he received more attention from her, the soiling and day-wetting stopped, although bed-wetting continued until he was 5 years old.

When he was 4, he started kindergarten, but was very negativistic. During this year, he suffered from mumps. Also, the mother was away from home for about two months.

Parental Attitudes.—The maternal relatives, particularly the grandmother, disliked the adopted children and the patient most of all. He had been named after his maternal grandfather. When he was 2 years old, the mother and the grandfather had a violent quarrel which lasted about a year. The mother changed the patient's name and even had the engraving on his silver dishes changed. At this time, the child seemed confused as to what his name really was, but became accustomed to the new one after some months. When the quarrel was over, the mother changed the child's name again, but not the engraving on the silver, and the patient had some trouble explaining to curious adults why his silver was engraved with a name different than his own. During and after the quarrel, the mother displaced much of her hostility to her father onto the patient. She did not want to look at him, seldom spoke to him, and was constantly cross and irritable with him. Even her visits to him in the hospital were made grudgingly, as was the attention required by his braces and casts. On one occasion, the patient told his aunt he did not wish to go back to live with his mother because she hated him and did not want him in the house. The father liked the children, but he, a business man, was not home very much. The parents often went on

long trips, leaving the children with the governess who was a rather strict Englishwoman and who preferred the younger boy.

The child's symptoms indicate that he suffers from anxiety hysteria, for he has a great deal of anxiety, e.g., his numerous fears and his social insecurity; he has hysterical conversion symptoms—anorexia, constipation, and attacks of vomiting. He shows obsessional reaction formations in his excessive neatness and stuttering.

The history shows certain important situations, reactions to which form the basis for his illness. These are:

1. His ill treatment by his mother
   The frequent and long absences of both parents
   His nurses' attitudes toward him and their frequent changes
2. The fact that he is an adopted child
   His early attendance at schools
3. The adoption of his younger brother
4. The neglect and partial starvation in his early infancy
5. The long period of inactivity produced by his braces and his operation

TREATMENT

If his illness is to be cured, it is necessary to learn how he really felt and reacted to these experiences, what sufferings he thought he had undergone because of these reactions, and what limitations and defenses he had developed lest such reactions and the associated suffering return. In order to do this, it is necessary to know the child very well, and at his age this knowledge can be obtained best through the medium of his play.

In the first session he knocked on to the floor all the female toys, and when he heard a maid going by the playroom, he made derogatory remarks about her. This behavior indicated that his main difficulty was with women and fitted in perfectly with the known facts that his mother had treated him badly. Another example that illustrated this also occurred in the early sessions. He had a doll girl and boy play in a yard. The boy hit the girl and was punished by being forced to stay outside away from her.

In the next session we had to wait because another person was using the playroom. The patient tried to see who was there. When we got into the room, I asked him if he were not very angry at the people who had kept us waiting. He denied this but immediately got a cap gun and pretended he was shooting his own fingers off. Then he drew a picture of a boat on the blackboard and said that was the boat in which he was going to England and that he would leave behind everyone he knew. Following this interview, he went home and had an attack of vomiting. These sessions showed that he had two reactions to a jealousy situation:

1. He felt it would be better for him to injure himself or to go away than to express his hostility for another child, either actually or verbally.

2. He felt a strong desire to be the center of attention, expressed in an oral way (to be fed by the mother), but had to keep this desire unconscious and represented it by its opposite, vomiting.

There he seemed to have three main problems:

1. His great desire to have his mother love him
2. His fear to express this desire openly lest it make him feel hostile and jealous of the real objects of her affection
3. His fear to allow himself either to feel or to express his hostility lest his mother withdraw the little love he now received.

Unable to express directly his desire for his mother's love, he was forced to express it in a regressive, infantile manner—as a desire to be fed. When such ideas became too disgusting to him, they appeared as attacks of vomiting.

As can be seen from the history, he was partly starved as a young baby, and as a consequence he has never been able to separate the ideas of being loved from the ideas of eating. This was well illustrated in a number of interviews. Although he had plenty of toys at home, he demanded that I let him take some of my toys with him and became quite angry when I refused. He also complained that his mother did not give him the things he wanted. A little later he spent a session in which he fished and I was to eat the fish he caught. He alternated this with attempts to spank me, as if he felt I was not understanding what he was dramatizing. Then he asked me to fish and give him fish to eat. Still later he requested that I buy him some candy. I promised to do so, but did not. He accepted my apology but immediately began to talk about animals, particularly turkeys having no heads, but seemed afraid to express any open anger about the situation. After I did bring him candy, he brought me chewing gum. These illustrations show definitely that he equated eating with loving and that this equation was the basis for his attacks of vomiting. His relationships with other people were on an infantile level, i.e., in such a relationship his main desire was to receive numerous material or actual expressions of love.

This desire to be loved was represented in a regressive manner because, if expressed in any other way, it would bring to the fore his hatred of his rivals and his fear of that hatred. At first he depicted his difficulty as follows. In a number of sessions he would prepare soldiers to play football or to make war, but never was he able to carry the game to its conclusion of one side's attacking the other. This inability, which appeared also in his passive behavior, in his need to be the center of attention, and in his dependence on God, i.e., he had told his mother that God was with him all the time, was the result of a conflict in his mind. He was afraid that if he were angry he would not be loved as he wished to be.

The anxiety about his aggression began to appear in his play and in his relationship to me. He told me that his things were better than mine. He played that a bad man attacked and hurt a captain. The latter was put to bed, and the bad man killed him. Since he told me after this play that he had been ill with a vomiting attack, it was evident that he was the captain and I, the bad man who would kill him; i.e., he blamed me for his hostility. He tentatively shot at me and then went and hid himself. He started to play that he and I were fighting but could not go through with it. In the next interview his play showed his feelings of jealousy. Two nurses talked together, and then the captain attacked them. As a reaction to this expression of jealousy, he wished to bring his brothers to the next interview.

There now ensued a number of sessions in which a pirate was isolated from all the other soldiers, particularly from the female figures, and jailed and punished for making a noise at night. He said he was the jailer and I, the pirate. There were many sessions in which this play was repeated. At this same time I often had to be on his side against the bad people, but he coupled this with a statement that he liked his home and did not like being with me. About the time the younger brother had a tonsillectomy, he also played the Big Bad Wolf. I had to be the wolf and eat him up and then I was killed. He had a cold of which he notified me and told me I must stay away from him lest he breathe in my face and infect me. Soon after he deliberately did this. However, he said he wanted to be sick so I would have to come and look after him. His hostility to me became greater until he expressed the wish to kill me and told his mother that he actually had. This behavior was discussed with him as real feelings of hostility to me as a representative of his father and as real feelings of fear of this hostility. I erred, however, in my statement of the person whom he hated. The bad pirate was his younger brother.

Turning back to the history and to his behavior, it was now possible to see what had happened. He had been very jealous of his younger brother when the child was adopted, but was so insecure with his mother who was mean to him that he could not express it except through the regressive acts of soiling and wetting. These were acts of hostility to the mother and an attempt to get all her attention in the way the younger brother did. As the younger brother was a show-off and actually the center of attraction, and as his annoyance at this was suppressed by his mother, he could do nothing except avoid playing with him; when taken to a party he feared lest the hostility suddenly appear in his relations with other boys and cause him to be disliked. The play also portrayed a real present situation at home. The younger brother would wake early in the morning, wake the patient and do things to make him be noisy, for which the patient was punished. He had to take the younger brother to school. On the way they had to cross a busy inter-

section. The younger brother delighted in trying to run out in front of the cars, and the patient was filled with fear lest he be hurt and the patient be blamed. I discussed this whole situation with the patient, telling him that I thought these responsibilities very unfair, and that, although he felt afraid to boss his brother, it was quite all right for him to do it. I also discussed the situation with the mother who, although well educated and intelligent, had not realized what was happening. Through my discussion with her, she told me that, although she had always preferred the younger boy and could not stand the patient, she felt her attitude was changing, for she could see the younger's faults and patient's good points. She decided to put the patient in a separate room and to deal with the younger boy's behavior. Following this, there was considerable change in the patient. He was able to assert himself more at home and got along very well and happily at parties, joining in the fun and having a good time. He began to stand up for his rights with his brothers. He had no fears, and all eating difficulties had ceased.

The problem of his suppressed jealous hatred of his younger brother and more deeply of his father overlay a more fundamental problem, his insecurity with his mother and his adoption. He began to talk quite often about his mother's selfishness, meanness, and bad treatment. At the same time he constantly made requests of me, and when they were refused, he began to retaliate by trying to destroy my things. From early in treatment he had been interested in playing many variations of hide-and-seek. While he drew, I must hide my eyes and not look at the object drawn until finished. While I slept, he hid under the sand table and made noises, the source of which I had to find. Sometimes in my search I would be caught in a trap, sometimes shot, or sometimes my legs would be injured and I would have to go to the hospital. Sometimes he hid and I had to search for him, but when I found him he was very ill or dead or in the hospital. There was also a series of sessions in which either I had hurt legs and he looked after me or he had hurt legs and I visited him, did things for him, and brought him presents. At times he behaved cruelly to me while I was ill. He also played that he swam with his mother, but always either she or he was drowned.

It can be seen from this play that the patient had much anxiety concerning the loss of his real mother, the frequent changes of nurses, his mother's absences, and her coldness to him. He reacted to these experiences either by feeling actively hostile and wishing to hurt her, i.e., by sadistic impulses, or by desiring to be hurt by her, i.e., passive masochistic longings. These longings to be hurt in order to get his mother's attention were based upon his hospital experiences. He now admitted definite memories connected with it and with her visits to him which he had denied before. The cruel treatment of me while ill was a real retaliation on his mother for the cruel treatment she had given him

during his illness. About both sets of feelings he had much guilt. He had guilt about his sadistic feelings to her because they were in conflict with his masochistic longings and because he feared that, if he expressed them, she would go and leave him in utter loneliness. He had guilt about his masochistic longings because they conflicted with his masculine pride and because he feared to arouse his jealous hostility to his father and siblings. At the height of the conflict between his sadistic, hostile feelings to his mother and masochistic longings for her, his speech became much worse and then gradually improved.

Each group of reactions depicted in his play was discussed with him in terms of his relation to his present mother and his real mother. The hide-and-seek games were followed by a series of shows in which he acted clownishly and expected applause. This was in decided contrast to his earlier behavior of never being able to recite in school or at home and was an identification with the show-off younger brother which had been impossible as long as the patient had feared the extremely hostile elements in such an identification. During the show he also had sessions in which his father was hurt, and finally there was an entire session in which he severely and vehemently injured a man. This man was the father and the younger brother.

Two successive sessions were interesting in showing the change in behavior following an interpretation. He was playing the noise-making games at night in which I had to find him and then he attacked me. At this point I discussed with him the situation between his mother and himself, pointing out her cruel behavior to him when he was younger and the reason for it, i.e., that she was not hostile to him but to her father and had taken this resentment out on him. He listened silently, and without any reply the hour came to an end. At the next session his behavior changed. He stuttered much less and began busily to plan a war. He made his arrangements quickly and then utterly destroyed the opposing army with great pleasure. In this he was stating that no longer was he afraid of losing his mother's love if he were aggressive, but knew that he could express aggression and jealousy and still feel secure with her.

COMMENT

This child's neurosis had involved all phases of his life, physiologic, social, and habit patterns. His symptoms were an attempt to solve his emotional conflicts. These were his fear and guilt about his hostility to his younger brother and to his father and his fear that he might lose all his mother's love if he expressed his strong love for her and his equally strong resentment at her coldness. These conflicts were kept active constantly because his longings for his mother's love were never satisfied. His longings were not excessive, but the mother's unloving, antagonistic attitude gave no gratification for the child's ordinary need to be loved.

The case material indicates very clearly the importance of obtaining a detailed developmental history. When such a history is compared with the child's presenting symptoms and behavior and when the history is contrasted with the developmental history of a secure and loved child, the effect of the historical background upon the child's development becomes evident. Such a comparison also indicates the points where personality reactions, adverse to his real happiness, have been developed in order to try to make specific instinctual drives conform to unnecessary environmental limitations. This is of great importance, for, if the child is to be well and remain well, these personality reactions have to be broken down and new and more usable ones substituted. Without such a detailed developmental history, much time would be consumed in trying to understand how the child became as he is, for it is extremely difficult to get historical material quickly and with any accuracy from a young child.

The case material also shows the value of allowing the child to dramatize his emotional conflicts in his play. One of the functions of child play is to dramatize emotional conflicts so that the child can deal with them more adequately.

As the case illustrates, the dramatic presentations are correlated with the child's present reactions and his developmental history, and such correlations are discussed with him in detail. This enables the child to understand his reaction patterns which he has only felt before and, by understanding them and the reasons for them, to deal with his present life problems more according to their real nature and less according to his feeling patterns which had been formed as his only possible response to the previous difficulties of his life.

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Round Table Discussion on Nephritis

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1. Early Differential Diagnosis Between Postinfectious Hemorrhagic Nephritis and Chronic Nephritis

C. A. Aldrich, M.D., Winnetka, Ill.

Because it is so natural and logical to suppose that chronic nephritis is an aftermath or sequel of the ordinary acute nephritis, it seems almost presumptuous to adopt any other viewpoint. Yet this is exactly what our clinical experience at the Children's Memorial Hospital has forced us to do. In this brief introduction I will try to make clear the steps which led us to so unorthodox a position.

From the beginning of our observations on nephritis, some twenty years ago, we called the first attack of renal symptoms acute nephritis, plus some distinctive term such as hemorrhagic, glomerular, or even parenchymatous. This latter term was soon abandoned when nephrosis entered the field as a separate entity, and the term need no longer be referred to here.

After about ten years of study of these nephritic patients, we found that it was fairly easy to distinguish three modes of onset: (1) a large number in whom the renal symptoms followed, or were coincident with, an easily demonstrable, acute, febrile infection; (2) a much smaller number in whom the initial symptoms appeared insidiously without any spectacular antecedent infection; and (3) a very small group in whom the nephritic symptoms appeared as a disastrous complication of a fatal streptococcic septicemia.

When these three groups were studied from a prognostic standpoint, the differentiation showed startling implications. The patients with the postinfectious history have made complete and permanent recoveries, almost to 100 per cent. The exceptions are: one patient known to have relapsed into chronic nephritis after a few years of intervening good health; two patients who had second attacks which healed as quickly as the first and who are now well; and several who continued to show albumin in the urine without other symptoms for periods of months or years, most of whom finally recovered and none of whom have as yet exhibited signs of true chronic nephritis. When it is remembered that our series comprises between 300 and 400 cases in this type, it does not seem an unpardonable exaggeration to say that these patients all recover.

On the other hand, those who had an insidious, noninfectious onset tended to run a chronic, downhill, ultimately fatal course. At one time we tabulated the

outcome of thirty-five such patients and found that thirty were dead and the five remaining were chronic invalids. With later changes in management, we have been able to tinge their prognosis a somewhat brighter hue, but we still hate to have a child enter with this insidious story.

All of the patients in the third group, the septicemic group, died of the sepsis, not of their nephritis.

When these observations began to be apparent about ten years ago, we attempted to segregate the chronic cases at the onset instead of waiting for their chronicity to become apparent with the passage of time. In this effort we were fairly successful, so that few mistakes were made. The characteristic points noted in the early days of the chronic disease were: (1) absence of antecedent infection; (2) a persistent edema lasting beyond the few days to a week or two seen in postinfectious nephritis; (3) a tendency toward early functional impairment as shown by the usual tests; and (4) evident chronic malnutrition. It was only a step from this to the hypothesis, which we still think likely, that the two conditions are separate entities from the start.

This attitude toward the problem led, it should be mentioned, to a search for causes other than infection in the etiology of chronic nephritis, and, in our clinic at least, to a marked reduction in the morbidity of the patients and to a few apparent cures.

2. Management of Edema in Acute Nephritis and the Nephrotic Syndrome

Lee Edward Farr, M.D., New York, N. Y.

Edema in initial acute nephritis is the result of failure of the kidney to eliminate normal quantities of salt and water in the urine. Loss of fluid to tissue spaces because of decreased osmotic pressure of plasma is usually not a factor. In terms of the filtration-reabsorption theory, anuria and oliguria may result from a decrease in the quantity of glomerular filtrate, excessive reabsorption of salt and water by the tubules, or a combination of both factors. In acute nephritis the principal factor appears to be a decrease in the glomerular filtrate. This follows a diminution in total renal blood flow. In acute nephritis the decreased renal blood flow is probably the result of afferent arteriolar constriction and plugging of glomerular capillaries by exudate. Histologic evidence supports this view. Indirect evidence of decreased renal blood flow has been obtained by studies of urea, inulin, and creatinine clearances in these patients. The evidence for excessive tubular reabsorption rests upon low urine chloride values even when the plasma chloride is above the threshold level of 90 meq. per liter. Disturbance of water reabsorption is shown by the failure of the kidney to balance water excretion to body needs. It may also be studied by assaying the urine for the presence of an antidiuretic principle. In general, however, one may say that, in acute nephritis, the primary disturbance appears to be a reduction of renal blood flow which affects glomeruli and tubules equally, and that the tubular disturbances as a result of this decreased blood supply are, in some respects, no greater than those seen in patients having normal kidneys with corresponding reduction in glomerular blood flow.

With this hypothesis, restoration of normal kidney function in acute nephritis rests primarily upon restoration of normal glomerular blood flow. With an adequate blood supply coming from the glomeruli to the tubules, reabsorption will return to more normal levels. If the kidney failure in acute nephritis is the result of changes in renal blood flow, therapeutic agents acting primarily upon the tubular cells may be expected to be of little assistance and may even be decidedly harmful. It is useless to expect results from a diuretic, such as the mercurial diuretics, when the renal blood flow is decreased to a degree that the unconcentrated glomerular filtrate is insufficient to provide necessary water and salt elimination. Urine volume can never exceed glomerular filtrate volume, and,

in fact, never equals it. Consequently, our therapeutic problem is one of finding measures which will promote increased renal blood flow. This definitely cannot be accomplished with any diuretic known at present. It is our belief that the use of diuretics in acute nephritis should be limited to urea, and that should be used by seldom. Unfortunately, intravenous fluids alone will not suffice to restore renal blood volume. There is no evidence that quantities of fluid in excess of metabolic requirements have any favorable effect upon renal blood flow other than the negative one of preventing shock. On the other hand, sharp restriction of fluid intake can result only in further difficulties for the patient, for in the train of dehydration is shock which will exacerbate the original renal disability.

Until more specific therapy is available our efforts should be directed at maintaining normal blood volume, preventing dehydration, and avoiding excess fluid administration. Transfusion, infusion, and hypodermoclysis all have their uses in such efforts. They do not offer us any certain road to recovery, but they do permit us to satisfy in a limited fashion some of the patients' metabolic needs. If we err in any direction, let us err on the side of too much, rather than too little fluid. The fluid needs of these patients are certainly no less than those of normal patients with equally severe infections. If the patient can be maintained in a satisfactory state until natural recovery processes have an opportunity to assert themselves, he then will be in a position to regain more rapidly his normal function.

In the nephrotic syndrome the principal factor in causation of edema is a decrease in the osmotic pressure of plasma. This is the result of hypoproteinemia. The decrease in plasma protein occurs almost entirely in the plasma albumin fraction. In maintenance of osmotic pressure the plasma albumin is much more effective than globulin because it is a smaller molecule. The decrease in osmotic pressure favors a rapid passage of water and diffusible ions from the vascular system to extracellular spaces and, at the same time, a retarded transfer of water and ions from tissue spaces to the vascular system. Under these conditions, equilibrium between extracellular fluid and plasma is attained only when there is a considerable increase above the normal volume of extracellular fluid. Associated with this extrarenal diversion of fluid from the vascular system is a decrease in excretion of salt and water by the kidney. Although in many of these patients there is also a decrease in renal blood flow, the volume of glomerular filtrate is large enough to permit excretion of adequate quantities of water. It is a common observation that, when patients are in the terminal stage of chronic glomerulonephritis, the plasma proteins rise above the edema level and the edema disappears. If the primary difficulty were reduction in glomerular filtrate volume to exceedingly low levels, this phenomenon could not occur. It is also strong evidence that the edema of nephrotic syndrome is primarily hypoproteinemic in origin. In the nephrotic syndrome tubular overactivity plays a definite and important, although we believe secondary, role in maintenance of the edema. These patients reabsorb salt almost completely from the glomerular filtrate, and with the reabsorbed salt goes water. Thus there is returned to the general circulation an excess of salt and water which is too large for the lowered osmotic pressure of the proteins to keep within the vascular system, and the loss of fluid to extracellular spaces is thereby exacerbated. The reabsorption of water in these patients is largely determined by the salt reabsorption. Although water alone will not increase edema, even when there is little or no increase of urine volume following its administration, salt administration will markedly increase edema. Edematous patients of this type will show evidences of dehydration on a sharply limited fluid intake even when edema is massive.

Treatment of the edema in the nephrotic syndrome should be based upon procedures which will correct the hypoproteinemia and prevent excessive reabsorp-

tion of salt. We believe that promotion of synthesis of plasma albumin can best be stimulated by feeding a diet optimal in protein content for assimilation of nitrogen. Studies which we have carried out in our clinic indicate that the optimal protein diet for nephrotic children is the same as for normal children. This indicates that the protein content of the diet should approximate about 3.5 to 3.8 Gm. per kilogram of ideal body weight for children from 1½ to 3 years of age; about 3.2 Gm. per kilogram for children from 3 to 6 years; and a gradual decrease with increasing age to 2.0 Gm. per kilogram for 12-year-old children. Results obtained by such treatment may be slow in appearing, and months may pass before appreciable progress has been made. However, when the plasma albumin is above the critical edema level for children, which is 1.2 Gm. per 100 c.c., we have found that usually the child can be induced to deliver his edema and can be maintained edema-free by severely restricting his salt intake so that it is not greater than his salt elimination. Practically, the salt intake cannot be restricted to less than 1.0 Gm. a day when an adequate protein diet is offered. However, in our experience it is very rare that nephrotic children cannot be maintained edema-free with this amount of salt in the diet. When the plasma albumin is above the critical level, diuretics may be expected to be of value in relieving the edema. We believe the diuretic of choice is urea. Mercurial diuretics act upon the tubular cells which are already injured in these patients. Their action is uncertain, and they offer no advantages over urea except in the ease of administration. When the plasma albumin is below the critical level, even urea is of no value in our experience, and it is necessary to wait until the plasma albumin reaches 1.2 Gm. before utilizing more vigorous measures. Once the child has been freed of clinical edema, we have been able to maintain him edema-free by restriction of salt intake alone until the plasma protein level has risen to near normal levels when salt may again be given safely in normal amounts. This treatment lacks the dramatic rapidity of diuresis seen in treatment of cardiac edema with mercurial diuretics. In our hands, however, it has been quite satisfactory and has had the added advantage of our knowledge that in using such measures no further insult had been inflicted upon an already injured kidney.

3. The Use of Sulfanilamide in the Treatment of Acute Nephritis

Acute nephritis is nearly always associated with a hemolytic streptococcus infection. Elimination of infection has always been a major part of the treatment of acute nephritis. By controlling the inciting infection, we seek to prevent further renal injury and to favor recovery from the renal injury already sustained. Until recently, measures available against the infection were generally unsatisfactory. In the past few years, sulfanilamide has proved to be an effective therapeutic agent in the treatment of hemolytic streptococcus infection. As with all potent drugs, the effects are not limited to the bacterial invader alone. The drug is also toxic to some degree to the patient. Reports on the pharmacology of sulfanilamide have been numerous, and it is not necessary to discuss those aspects now. I shall touch on this point only in relation to the effect of the drug on kidney function.

The value of sulfanilamide in acute nephritis depends upon its effectiveness in controlling the infection which is inciting the renal injury. Although most infections associated with the onset of acute nephritis are streptococcal in origin, a few are not. We should first make certain that we are dealing with a hemolytic streptococcus infection. Evidence that the infection may be streptococcal in origin does not necessarily mean that sulfanilamide will be effective. If the infection is of a type which responds to sulfanilamide, such as adenitis, sinusitis, or bacteriemia, we may expect favorable results with drug therapy. If, however, the only evidence of infection is a throat culture positive for hemolytic streptococcus and there are no clinical evidences of acute infectious disease, the benefits from sulfanilamide are

uncertain. Because the drug is a powerful agent, there is a temptation to rely upon it alone. In dealing with nephritis we must be careful not to develop such an attitude. Sulfanilamide has no effect whatever in ameliorating the damage which has already occurred in the kidney when the diagnosis is made. All measures for the treatment of nephritis which have proved to be of value are just as necessary in the patient treated with sulfanilamide as in the patient in whom we can find no infection whatever in acute nephritis. Sulfanilamide is merely an adjunct to our therapy, albeit an important one.

When sulfanilamide is used, the dosage should be sufficient to permit of the attainment of a level in the blood which will ensure maximum effectiveness without overdosage. In dealing with patients without renal involvement, overdosage is unlikely. When, however, renal function is decreased, the excretion of sulfanilamide is also diminished. The excretion of sulfanilamide is similar to urea and is impaired to about the same degree. In nephritic patients it is safe to give the usual initial dose and to maintain the normal dose for the first twenty-four hours. After this interval, smaller than normal maintenance doses should be given whenever renal failure in any degree is present. The decrease in maintenance dosage should be proportional to the decrease in renal function. Probably maximum effectiveness of the drug is reached with a blood level of from 6 to 10 mg. per 100 c.c. Except in severe renal failure, the determination of the blood level once or twice a week should suffice to determine the maintenance dose. Once this has been determined, it is safe to continue on this dosage unless further renal failure develops. When we give the drug to our nephritic patients, we do not give alkalies simultaneously. In these patients there frequently exists an inability to excrete fixed base, and free administration of sodium bicarbonate may result in an alkalosis which is exceedingly difficult to treat. We have not found the drug to produce clinical signs of acidosis in our patients with this mode of administration. We have not seen gastric upsets more frequently than when alkali is given simultaneously. If the patient is unable to retain sulfanilamide because of gastric irritability, it is better to use an intramuscular preparation and abandon oral medication until nausea and vomiting have subsided. It is more difficult to maintain the blood level in this way and a somewhat larger dose may be necessary, but this should be given without hesitation.

We have never seen any adverse effects upon renal function result from the use of sulfanilamide under these conditions. We have given it to some of our patients for as long as three months without interruption with no ill effects on urea clearance or urine sediment. Smadel and Swift, reporting in the November, 1939, number of the *Journal of Clinical Investigation* a study on the effect of sulfanilamide on nephritic rats, came to the conclusion that the drug in therapeutic doses did not have any deleterious effect on the kidney.

If it becomes necessary or desirable to carry out operative procedures on these patients during the period of acute nephritis, these can usually be done without exacerbating the renal lesion by preliminary treatment with sulfanilamide. In the event of an infection such as an acute sinusitis, the patient will have fewer renal complications if sulfanilamide is used for a day or two before surgical treatment of the sinusitis is begun. If immediate operation is indicated and previous drug therapy has not been begun, a larger than usual initial dose should be given, but the results under these circumstances may not be as good as when a satisfactory blood concentration has been attained prior to surgery. In routine tonsillectomy after acute nephritis has subsided, but before complete recovery has taken place, acute exacerbations of the nephritis can be held to a minimum by giving the patient sulfanilamide before and immediately after the operation. Sulfanilamide therapy under these conditions makes it no less imperative that the surgeon be as gentle as possible in carrying out the necessary procedures.

If we limit our use of the drug in nephritis to the control of inciting infections in which it is active, and bear in mind that it has no direct therapeutic effect upon the already damaged kidney, no difficulties should beset its use. Its benefits are limited to prevention of further renal damage by infection. The injured kidney must still be protected from other types of assault by our general therapeutic attack and must not be forgotten in our haste to eliminate infection.

4. The Treatment of Postinfectious Hemorrhagic Nephritis
Dr. Aldrich

The Cerebral Symptoms.—While the therapy of the spectacular cerebral symptoms of postinfectious hemorrhagic nephritis has, during the past fifteen years, improved to the point where few, if any, patients now die of this condition, confusing situations still arise to plague the clinician. Modern treatment is based upon two main concepts: (1) that the immediate cause of the symptoms is *cerebral*, due either to edema of the brain or to vascular spasm of vessels within the skull; and (2) that the underlying or basic cause of the symptoms is an *intoxication* by an infectious process.

The recognition of the first concept has led to specific therapy with magnesium sulfate whether the clinician believes in the edema or in the spasm theory of pathogenesis. Therefore, it can be stated that the vast majority use this drug as a routine when the onset of these symptoms—rising blood pressure, nausea, headache, eye sensations, convulsions, or coma—is noted. This routine may be briefly outlined as follows:

1. In cases where the patient is *conscious* and edematous, oral administration of the saturated solution in doses of from 1 to 5 ounces daily.
2. In unconscious or vomiting patients,
   (a) intramuscular injections of 50 per cent magnesium sulfate solution, 2 to 4 c.c. every 4 to 6 hours until symptoms subside;
   (b) in more desperate cases, intravenous injection of 2 per cent solution very slowly until the blood pressure drops to normal.

Those who hold that cerebral edema causes the symptoms ascribe the beneficial results to reduction of edema in the brain by the salt action of magnesium sulfate according to the theory of M. H. Fischer. Those who believe that vascular spasm is at fault point out that this drug quickly relieves such spasm. It is a fortunate and rare coincidence that those who favor such widely diverging theories can unite so amicably on the technique of therapy.

In addition to this method of treatment, however, the other concept, that the basic cause is an *intoxication*, has led to quite important therapeutic considerations. The most important of these, to my mind, is the fact that it has led to free allowance of fluid to patients with postinfectious nephritis, whether or not they show these distressing symptoms. This has undoubtedly prevented the complication in many instances and has decreased the mortality tremendously.

In the second place, it has directed our attention to the *infectious source* of the disease, the treatment of which has just been discussed by Dr. Farr. I should like to point out a frequent source of confusion to those handling such patients. Cerebral symptoms often occur while there are still evidences that the infection is still somewhat active. This raises the question as to whether the brain symptoms or the infection should be attacked first. If the infection is amenable to simple surgical attack, this should undoubtedly be resorted to. In this event magnesium sulfate can also be used if indicated. Often mastoiditis and otitic and other abscesses are seen which can safely be handled in this way. But, unfortunately, it is more frequently true that the source cannot be so easily eradi-

cated; and in these instances one is faced with the problem of whether to use sulfanilamide in direct attack on the infection, or to use magnesium sulfate to relieve the threatening cerebral state. Both cannot be used because of the incompatibility of the drugs.

In several cases in which I have had to choose one horn of this dilemma, sulfanilamide has been used, and in all such instances the result has been most satisfactory. Relief from the intoxication has caused a prompt amelioration of the cerebral signs. Only in patients with urgent symptoms such as deep coma would I use magnesium sulfate first.

The problem of the treatment of such patients, then, may be summarized as follows:

1. Where the original infection is still active, use surgical measures where they can be easily and simply applied; use sulfanilamide in others.

2. Where the original infection is quiescent, use magnesium sulfate by mouth, muscle, or vein.

3. In all cases allow free administration of fluids.

DISCUSSION

DR. D. D. KOVAN, DETROIT.—In what group would you put chemical nephritis?

CHAIRMAN ALDRICH.—In a rare category by itself.

DR. P. S. ASTROWE, KANSAS CITY.—If cardiac factors produce symptoms, how do you handle them?

CHAIRMAN ALDRICH.—By use of 50 per cent glucose intravenously plus bed rest, etc., and prescription for hypertension if present.

DR. F. J. CORPER, CHICAGO.—What about the use of immune serum in the infectious type of nephritis?

CHAIRMAN ALDRICH.—This may be a valuable aid in those types which resemble scarlet fever.

DR. J. B. STONE, RICHMOND.—How soon after acute nephritis is it safe to remove surgical foci of infection, particularly to perform a tonsillectomy?

CHAIRMAN ALDRICH.—As soon as albumin and blood are no longer found in urine.

DR. T. O. ELTERICH, PITTSBURGH.—Describe the method to arrive at the proper dosage of sulfanilamide in postinfectious nephritis.

DR. FARR.—We use a dose of 0.1 Gm. per kilogram ideal body weight (average weight for height and age) or ¾ grain per pound. One-quarter of the total daily dose is given initially and repeated in four hours. One-eighth of the total daily dose is then given every four hours until the entire dose has been taken. We then determine the level of sulfanilamide in the blood. This should range from 6 to 10 mg. per 100 c.c. In patients with acute nephritis with oliguria and nitrogen retention, we give 0.05 Gm. per kilogram as a maintenance dose, one-half of which is given every twelve hours. After two days we redetermine the level in the blood and increase or decrease the maintenance dose accordingly. Once a satisfactory level has been attained and maintained for one week, it is necessary to check the blood level only occasionally. The excretion of sulfanilamide parallels inversely the severity of nephritis, and the dose may be decreased in proportion to the decrease in urea clearance or the rise in blood urea nitrogen or nonprotein nitrogen. The fifteen-minute phenolsulfonephthalein test is satisfactory to determine the degree of renal

impairment. If the phenolsulfonephthalein is normal, the regular daily dose may be used. If the phenolsulfonephthalein excretion is diminished, the sulfanilamide dosage should be decreased accordingly.

DR. R. C. BOND, WHEELING, W. VA.—Please sketch out the treatment with urea.

DR. FARR.—Urea to be effective as a diuretic must be used in fairly large quantities. We give a 5-year-old child from 40 to 60 Gm. a day, divided into three or four equal doses. Lemon juice, grapefruit juice, or grape juice makes a satisfactory vehicle. We give fluids ad lib. during the urea treatment. If there is renal insufficiency, it is necessary to watch the blood urea nitrogen. If the blood urea nitrogen rises over 20 mg. per cent, the urea dose should be decreased or preferably discontinued until an improvement in renal function has occurred. The patient should be kept on a low salt diet throughout the period of urea administration. We have given it daily for as long as six weeks.

DR. J. D. CRAIG, NEW YORK.—Can you explain how a straight nephritis takes on nephrotic changes?

CHAIRMAN ALDRICH.—I have not seen this take place.

DR. FARR.—The term nephrotic has only a clinical meaning. If a patient with chronic hemorrhagic Bright's disease develops severe hypoproteinemia and inability to excrete salt, he will develop edema and may properly be described as a nephrotic type. These changes in such a patient should be regarded as a manifestation of nitrogen wasting. This does not indicate there has been any fundamental change in the nature of the disease.

DR. W. E. NELSON, CINCINNATI.—Is there any way to determine an adequate protein?

DR. FARR.—I presume you mean dietary protein. Optimal protein content of the diets can be determined by nitrogen balance studies. We have found this optimal value in our nephrotic children to be approximately the same as for normal children. The diets we give contain protein in the amounts I mentioned in my original discussion.

DR. J. A. SCHOONOVER, DENVER.—You mention that urea is the only treatment. Do you include the tubule extracts?

DR. FARR.—Urea is not the only diuretic for use, but we believe it is the diuretic of choice. We have had no experience ourselves with tubule extracts, but some of our patients have been so treated before coming to us. In these instances, the course of the disease appeared to be unchanged.

DR. STONE.—What do you mean by salt-free diet?

DR. FARR.—A diet with no free added salt and containing only foods relatively low in salt content. For practical purposes, we consider a diet containing 60 Gm. of protein and from 1 to 1.5 Gm. of salt as "salt-free."

DR. RUTH BERREY, BIRMINGHAM, ALA.—Is the prognosis in infectious nephritis as good in cases in which there have been two or three attacks?

CHAIRMAN ALDRICH.—Yes, but second and third attacks are quite rare.

DR. K. BLANCHARD, EAST ORANGE, N. J.—Is it always a clean-cut diagnosis whether or not you have postinfectious nephritis?

CHAIRMAN ALDRICH.—No, but if the points spoken of are remembered and time is taken in making the diagnosis, few mistakes are made.

DR. BOYLE.—Described a patient with chronic nephritis without an infectious history who two years later developed scarlet fever, following which the kidney findings were the same. A case which would probably be labeled postinfectious nephritis if the history was not known?

DR. CRAIG.—In your opinion, why do some cases of acute infectious nephritis clear up promptly and others not, and is there any prevention?

CHAIRMAN ALDRICH.—All of our cases clear eventually, using the word "all" with the usual care. Why some have prolonged albuminuria we do not know.

DR. VIVIAN TAPPAN, TUCSON.—How frequently is pneumococcic infection seen?

DR. FARR.—We have had very few patients with acute hemorrhagic Bright's disease in which the initial infection was caused by the pneumococcus. On the other hand, in over 95 per cent of our nephrotic patients, that is, in patients with an insidious onset of their disease with edema as the chief manifestation, we have been able to isolate consistently pneumococci from the throat flora.

DR. STEWART.—How much of a factor, if any, is edema of the kidney?

DR. FARR.—I do not believe edema of the kidney is an important factor. Decapsulation has been recommended as a treatment for anuria, and although at times favorable results have been obtained, frequently no benefit was observed. There is a possibility that renal denervation would be equally effective. Until further experimental data are reported, the question cannot be answered definitely.

DR. SCHOONOVER.—Are there any other measures aside from salt restriction which will increase the blood supply of the kidney?

DR. FARR.—Salt restriction does not increase renal blood flow. Salt is restricted in these patients because they are unable to excrete it. If salt depletion occurs in these patients or in normal persons, there is a decrease in renal blood flow. A high protein diet will increase renal blood flow in dogs, and we have observed the same phenomenon in our nephrotic children.

DR. SCHOONOVER.—How about local heat?

DR. FARR.—Local heat probably does not penetrate to the kidney. Dr. I. H. Page, using diathermy over the kidney region, was unable to detect any change in the urea clearance.

DR. L. F. HILL, DES MOINES.—It is my impression that the restriction of salt is not so important in acute nephritis as in nephrotic syndrome.

DR. FARR.—That is essentially true. In acute nephritis salt need not be sharply restricted unless there is rapidly increasing edema or rising levels of serum sodium and chloride.

DR. SCHOONOVER.—What is the fluid of choice to be given intravenously to patients with edema?

DR. FARR.—Glucose solution. Recently we have also been giving amino acids intravenously.

DR. SCHOONOVER.—What is your reaction to acacia?

DR. FARR.—I would not use it although it does increase the osmotic pressure of blood plasma. We have observed several severe reactions following its use, with uremia as a sequel. Acacia also depresses the rate of formation of serum protein.

DR. MOORE.—Would a transfusion of blood serum be as good as administration of amino acids?

DR. FARR.—No. The effect of transfusion is very temporary because following transfusion there is almost uniformly an increase in proteinuria to an extent that an equivalent additional loss of protein occurs in the urine within forty-eight hours. The amino acids are not lost in the urine but are metabolized, as is dietary protein.

DR. MOORE.—How about lyophile serum?

DR. BOYLE.—Even this does not usually increase materially the plasma protein, although it is frequently followed by diuresis.

DR. BROWN.—I have a patient, a child, who had an acute hemorrhagic nephritis in May. She still has a slight hypertension and albumin and red blood cells in the urine. Is she likely to develop chronic nephritis?

DR. BOYLE.—She may still recover. I seldom see it develop following an acute nephritis.

DR. FARR.—If after four months the urea clearance and the maximum nonprotein specific gravity of the urine have returned to normal, there is an excellent chance for complete recovery even though albumin and red cells still persist in the urine. If the urea clearance has not improved within four months, it is likely that the patient will progress into the chronic active stage of hemorrhagic Bright's disease.

NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, OHIO, NOVEMBER 16-18, 1939

Round Table Discussion on Nontuberculous Chest

Chairman: Isaac A. Abt, M.D., Chicago, Ill.
Assistant: Paul Holinger, M.D., Chicago, Ill.
Secretaries: Jerome Glaser, M.D., Rochester, N. Y.
Tom Mitchell, M.D., Memphis, Tenn.

CHAIRMAN ABT discussed the scope of the round table discussion and introduced Dr. Paul Holinger of Chicago.

DR. HOLINGER.—Dr. Abt has very kindly asked me to assist him in this round table discussion and has suggested that the discussion be divided into two principal parts: The first, the consideration of laryngotracheobronchitis and lipoid pneumonia, and, the second, the consideration of nontuberculous chest diseases from the standpoint of bronchial obstruction.

The term "laryngotracheobronchitis" is a long one, but it is descriptive of the acute infection of the respiratory tract which is seen most frequently in infants and is characterized by intense inflammation of the mucous membrane of the larynx, trachea, and bronchi. The inflammatory process is usually accompanied by the formation of a sticky, gummy exudate which, together with the thickened mucosa, produces a severe obstruction in the airways. Dr. Abt has suggested that I briefly summarize the clinical picture and the method of therapy found to be most effective. The classical picture is that of a child, usually under 2 years of age, who develops a cold, a croupy cough, and a gradually rising temperature. He becomes restless as the dyspnea increases, and the indrawing of the suprasternal notch at the epigastrium becomes more marked. The picture may change rapidly as pulmonary findings reveal that the major bronchi have become occluded with exudate, and the child will turn cyanotic or ashy gray if the dyspnea is not relieved. One of the important etiological factors is the age of the patient; the greatest number of cases are seen in infants under 2 years of age. There is a marked seasonal variation, with the largest number of cases seen during fall and spring, from October to December and from March to May. The type of organism responsible for the condition has received a great deal of discussion and study, and while the infection is fairly generally considered to be a streptococcic type, our experience, namely, that tracheal and laryngeal smears and cultures have revealed pure growths of staphylococci, has been confirmed by many others. The pathology, however, is that of a streptococcic type of infection of the very loose supra- and infraglottic tissues. This is accompanied by an invasion of the submucosal layers of the trachea and bronchi and finally a destruction of the mucosa and occlusion of the bronchi by fibrin and purulent exudate. The treatment may be divided into two factors: the management of the obstruction to the airway and the management of the toxemia. It is essential that the highest type of teamwork exist between the pediatrician and the laryngologist in handling both these factors. The general care is, of course, entirely a pediatric problem. It consists essentially of efforts to combat dehydration and to give the child as much rest as possible. We feel morphine and atropine are

definitely contraindicated. We have felt that one of the essentials of treatment consists in placing the child in a room where the temperature is kept between 74 and 76° with a humidity over 90 per cent. This is done by the use of mechanical humidifiers rather than by the use of a croup kettle. Because of the rapid liquification of secretions by this means, the obstruction is frequently relieved in a relatively short time. If relief of the respiratory embarrassment is not obtained, oxygen may be used; and, finally, surgical relief is indicated before the child becomes too exhausted. Tracheotomy represents the ideal surgical procedure in such a case, and a tranquil instead of an emergency tracheotomy may be done if the bronchoscope is passed into the tracheobronchial tree as a preliminary procedure. The advantage of the tracheotomy over the intubation tube is that secretion may be aspirated from the tracheobronchial tree very readily through the tracheotomy tube and there is no trauma of the larynx to produce chronic laryngeal stenosis.

CHAIRMAN ABT.—Would it not be well, Dr. Holinger, to emphasize that some of these cases have a peculiar, thick, ropy mucus which dries in the bronchus and forms crusts? Furthermore, what would you state as the indication for operation? Also what are the complications or sequelae of tracheotomy? Dr. Holinger will recall that in former times a long intubation tube and an aspirating tube, designed by Dr. Lynah at the Willard Parker Hospital, were used. Has the use of these been discontinued? Is intubation a lost art? In former days if one had a bad case of this kind, he would slip in a tube, and, if this relieved the patient satisfactorily, tracheotomy was obviously unnecessary. Intubation seems to have fallen into disuse. Why? This subject might be discussed and disposed of.

DR. HOLINGER.—There is no question that intubation as it used to be used is indicated if the obstruction is due to diphtheria, but in staphylococcic or streptococcic infections the tube is too apt to produce necrosis or ulceration of the larynx. Then one has to do tracheotomy later in order to extubate the larynx and to treat, possibly for many years, the chronic laryngeal stenosis which has developed.

CHAIRMAN ABT.—I advise against prolonged intubation. The tube should not be left in longer than from three to four days.

DR. E. H. SMITH, OGDEN, UTAH.—I have observed many intubations at Dr. Hoyne's clinic in Chicago, but from personal experience I feel that tracheotomy gives the best results.

DR. R. C. BOND, WHEELING, W. VA.—If one is in the home and the hospital is not close by, it may be well to intubate and give some relief until the child can be removed to the hospital for tracheotomy later, if indicated.

DR. L. O. HOPPE, ATLANTA.—I have seen a patient who, after tracheotomy, developed bilateral pneumothorax.

DR. HOLINGER.—This is one of the complications, as is subcutaneous emphysema. Sometimes the operation is done too low, allowing air to enter the mediastinum, or the skin is tightly sutured around the tube, causing a severe coughing spell to force air into the mediastinum or under the skin. An emphysematous bleb of visceral pleura may rupture to produce pneumothorax.

CHAIRMAN ABT.—Occasionally may not the surgeon in a hurried operation cut the posterior part of one of the cartilaginous rings in the trachea? In the little child they are very soft.

DR. HOLINGER.—This might follow as the trachea collapses in inspiration when the larynx is obstructed. Even the esophagus may be cut. These accidents

may be avoided by introducing a bronchoscope first. There is then no emergency, the emergency tracheotomy being changed to a tranquil one as air is piped into the lungs through the bronchoscope.

DR. L. PALMER, LOUISVILLE.—I feel that the early use of steam is of great value. I prefer tracheotomy to intubation and emphasize the importance of post-operative care, especially the use of suction.

DR. J. B. STONE, RICHMOND.—If one must use a steam kettle, does the resultant overheating of the room have any great disadvantage?

DR. HOLINGER.—I feel fairly certain that it does.

DR. J. J. GLABOFF, LOUISVILLE.—What about the use of iodine in small doses to liquefy the secretions?

CHAIRMAN ABT.—I have had no experience with this.

DR. HOLINGER.—It may liquefy the secretions. It also changes the taste of the child's fluids and may make him refuse to drink.

DR. L. E. HARRIS, CHICAGO.—I have had two cases of severe croup which were relieved with adrenalin. Some of these cases may be based on an allergy. It may be well to try adrenalin on them since it may be beneficial at times.

DR. J. GLASER, ROCHESTER, N. Y.—It is sometimes stated that the ordinary type of spasmodic croup is an allergic disease. I have been unable to relieve croup symptoms with ephedrine or adrenalin. I feel that it is a specific disease, possibly of virus origin. Dr. Holinger mentioned the difficulty sometimes encountered of determining whether a child's cyanosis is due to tracheal obstruction or to sulfanilamide or sulfapyridine now used so commonly as soon as a patient with laryngotracheobronchitis is seen. It would appear that the intravenous injection of methylene blue as described in the panel discussions yesterday would be of great value in determining this point.

DR. HOLINGER.—I believe it would be pretty difficult to give a severely dyspneic, restless, cyanotic 7- or 8-month-old infant a few cubic centimeters intravenously.

DR. P. E. WILLIAMS, HAMILTON, ONT.—What do you think of expectorants, such as ipecac, etc.? I think they are indicated.

CHAIRMAN ABT.—I used to use ipecac, apomorphine, tartar emetic, and other emetics, but not recently. Sometime ago I began the use of wet turkish bath towels hung up in the room to keep the air moist, and since then I do not feel the need of emetics. I do use some sedative, as, for example, large doses of the bromides.

DR. A. G. JACOBS, MEMPHIS.—Sometimes I have used from 10 to 15 drops of ipecac every ten minutes until emesis is produced, with happy results. The vomiting gives relief.

DR. H. C. CLARK, NEW ROCHELLE, N. Y.—Should bad cases of croup be given diphtheria antitoxin? Of what value are calcium and antipyrin?

CHAIRMAN ABT.—The expectorants, such as syrup of ipecac, which used to be much used in the treatment of croup, are rarely used any more. Calcium, antipyrin, and iodides are probably of little value. Keeping the air of the room moist is of great value, and good doses of bromide are of much assistance. In many communities the children have been protected by toxoid against diphtheria. In case of reasonable doubt, it is perhaps safer to give diphtheria antitoxin.

Paregoric may be of value in mild cases of ordinary croup. Such croup may be associated with a variety of diseases, but severe laryngotracheobronchitis may be due to a variety of mild infections or may be secondary to another disease such as influenza, measles, scarlet fever, typhoid fever, or, as has already been mentioned, diphtheria.

DR. G. MAKSIM, PETOSKEY, MICH.—I know of a fatal case of croup in which the only way diphtheria organisms could be recovered was by laryngoscopy.

DR. W. E. VAN ORDER, CHATTANOOGA, TENN.—Should one give diphtheria antitoxin or sulfapyridine when in doubt?

CHAIRMAN ABT.—The answer is diphtheria antitoxin. However, the fulminating onset of laryngotracheobronchitis will, in most instances, exclude the diagnosis of diphtheria.

DR. B. P. STORTS, TUCSON.—Is helium or oxygen of any value in this condition?

DR. HOLINGER.—We frequently use oxygen along with the steam inhalations to try to make the child more comfortable. The use of helium with oxygen is even more efficient than oxygen alone.

DR. GLASER.—The use of the new B.L.B. mask of the Mayo Clinic with helium and oxygen is probably the least expensive way for the oral or nasal administration of these gases. The apparatus may be bought or rented from the Ohio Chemical Company.

DR. M. P. BOROVSKY, CHICAGO.—If you saw a patient in whom operation was indicated, would you use oxygen or oxygen and helium, and does medicated steam do good? Are atropine and opium contraindicated? And is it important not to use them?

DR. HOLINGER.—We have used oxygen a great deal; when this is used, the humidity in the tent should be increased to prevent desiccation which the oxygen seems to aggravate. Unless surgical relief is absolutely imperative as a lifesaving procedure, we like to use a "test period" in oxygen. The helium is a good adjunct; it relieves exhaustion and the patient breathes easier. For a long time we have used no medication in our "steam" inhalations. Tracheotomy sometimes gets a bad name because it is done too late. If the patient is too cyanosed, oxygen and carbon dioxide piped into the lungs through a bronchoscope should be used continuously during the operation. We follow Jackson's advice against the use of atropine because of its drying effect. Morphine is dangerous to use for restless children with this disease, for it acts to depress their respirations and cough reflexes.

DR. A. GOLDBLOOM, MONTREAL.—It may at times be stimulating to inject a note of perversity into a discussion. I may do so now in discussing our experience with regard to the steam inhalations. We in the Infectious Disease Hospital have found the wide open window to let in cold air productive of more relief than the steam tent. This applies to both laryngeal diphtheria and tracheobronchitis. Intubation in the tracheobronchitis cases is never considered. The pathology extends too far down the bronchus for this to be of any benefit. Dr. Holinger's slides demonstrated this. Intubation increases this morbid condition and obstruction. Even a tracheotomy may not give relief. In the last two or three years, with sulfanilamide and sulfapyridine, the picture has changed; in twenty-four hours there is often complete relief.

DR. HOLINGER.—Nearly everyone uses sulfanilamide in these cases. The cyanosis is often misleading as it is impossible to say whether it is due to the obstruction or to the drug; for this reason, it is well to use it with care. If the culture shows

an organism for which these drugs are indicated, I would use them. It is interesting to hear about the improvement Dr. Goldbloom finds by placing the children in an atmosphere of the cold outside air. Our cases in the cold oxygen tent have not done as well as those treated with the steam inhalation.

DR. H. S. ANDREWS, LOUISVILLE.—What do you use as a sedative if the child is restless?

DR. HOLINGER.—We use no sedative if the obstruction can be relieved. Restlessness is an indication of increasing obstruction.

DR. W. W. NICHOLSON, LOUISVILLE.—Even after tracheotomy, some of these cases require sedatives. What sedatives do you prefer? Do you instill saline solution into the tube?

DR. HOLINGER.—We try to stay away from sedatives. Small doses of the barbiturates or the bromides are sometimes useful. The patient is kept quiet by aspirating the tube. The major portion of our set-up is the catheter on the aspirating pump. We do use saline or a weak soda-bicarbonate solution instilled into the tracheotomy tube to aid in liquefying the secretion, and thus reduce postoperative restlessness.

DR. L. H. SEGAR, INDIANAPOLIS.—Is cyanosis an indication for tracheotomy?

DR. HOLINGER.—Yes, but not the only one. Restlessness and principally exhaustion indicate a growing respiratory decompensation as well.

CHAIRMAN ABT.—What is the index showing the degrees of laryngeal stenosis? Is it cyanosis? Dyspnea?

DR. HOLINGER.—Retraction in suprasternal and epigastric regions, restlessness, later with exhaustion, and an ashy-gray color.

DR. E. P. RUSSELL, BERWYN, ILL.—Is the postural treatment of value if started early enough? Some use this treatment and seem to get good results with it.

CHAIRMAN ABT.—In these cases under discussion, it is of little value since the secretions are so thick and tenacious.

DR. CLARKE.—Does rickets have any local or constitutional relationship to croup?

CHAIRMAN ABT.—Rickets produces no essential changes in the larynx, although you will recall that laryngismus stridulus is a manifestation of tetany, a condition frequently associated with rickets.

DR. J. R. VONACHEN, PEORIA, ILL.—I feel that laryngotracheobronchitis is a specific disease entity. In the past two weeks I have seen seven cases, with five deaths. The two patients who recovered had tracheotomies. Pure cultures of *Staphylococcus albus* were obtained from the tracheotomy openings. I feel that intubation is contraindicated. What are the details regarding room temperatures and humidity in tracheotomized patients?

DR. HOLINGER.—Saturation of the air with moisture is very important. At the Children's Memorial Hospital special apparatus can raise the humidity in a room set aside for the treatment of cases of laryngotracheobronchitis to 90 per cent or over. The temperature of the room should be kept between 74 and 76°. The usual croup kettles heat the room too much. We have tried intravenous calcium without apparent benefit.

DR. WILLIAMS.—How do you carry on the treatment with saline after tracheotomy?

DR. HOLINGER.—A few drops are instilled into the tube with a rubber-tipped medicine dropper. The liquefied obstructing secretions are then aspirated by passing a catheter attached to an electric suction pump directly into the tube.

DR. A. B. SCHWARTZ, MILWAUKEE.—I wonder if there are not two kinds of infection in these cases. Certainly there seem to be some which are very mild and respond to any treatment and others which gradually progress, despite every treatment, to a serious condition. Perhaps it is a difference in the virulence of the organism.

DR. G. F. MUNNS, WINNETKA, ILL.—I have observed that laryngotracheobronchitis is most commonly seen when influenza is severe, and I have the impression that laryngotracheobronchitis may be a class disease. Cases are rarely seen on the North Shore, perhaps because the children get very early care at the onset of the upper respiratory infection which usually precedes this disease.

DR. J. M. MITCHELL, EVANSTON, ILL.—I have the same impression as Dr. Munns.

DR. HOLINGER.—I saw two deaths recently in North Shore children who had received early care. However, the great majority of cases do occur in the lower income groups.

DR. SCHWARTZ.—What is the mortality rate? What is the indication for removal of the tube?

DR. HOLINGER.—About 25 per cent. For the past two years ours has been less; then this year it jumped to 30 or 35 per cent. After two or three days the tube may be corked and, if the child breathes normally, the tube may be removed or a smaller one introduced. The indication for removal of the tube is the re-established airway through the larynx as demonstrated by the child's ability to breathe with a partially or completely plugged tube.

Lipoid Pneumonia

CHAIRMAN ABT.—Lipoid pneumonia has been observed most frequently in invalids and small infants with poor cough reflexes. Oily nose drops or oil by mouth or in the vomitus enters the trachea, and thus goes down into the lung. Sometimes it is seen after the use of mineral oil as a laxative, mineral oil in nose drops, instilled oil, or after cod-liver oil has been forcibly given, especially while the child is lying on its back. The symptoms in the infant are a slight fever, a failure to gain weight, and a cough of three or four months' duration. This condition has to be differentiated from pertussis which also has a slight fever and a similar white count. The x-ray picture is bizarre. Usually the involvement is in the upper lobes but is sometimes in the lower lobes in infants, and rarely in the middle lobe. Anteriorly one finds areas of compensatory emphysema. There is no single or characteristic picture. The course does not resemble that of an acute infection. On post-mortem examination, the alveoli are found to contain oil; oil-containing phagocytes may be found in the lymphatics and nodes, and in the liver, spleen, and kidneys. Fatty cell infiltration of the bronchi in this disease is sometimes found. One will also observe chronic proliferative changes with fibrosis and encapsulated oil in the giant cells. Usually there is a history of the administration of oil over weeks or months. The diagnosis is made by x-ray, or oil is

found in the sputum or obtained with the bronchoscope. Preventive treatment: Do not use oily nasal drops, and avoid the administration of oil to a struggling child.

DR. H. E. GALLUP, BROOKLINE, MASS.—When this condition was just beginning to be recognized, I assisted in the autopsy of an 8-year-old patient who had used the oil nose drops for a number of years. He had suffered a well-marked loss of weight and had a slight cough. At the autopsy we found the nodules and one large area of consolidation. We thought at first it was a carcinoma. Later, by microscopic study, the correct diagnosis was made.

DR. J. CHESNEY, KNOXVILLE, TENN.—Do patients with lipoid pneumonia die of the disease itself, or do they develop superimposed infections? Do any patients with lipoid pneumonia ever make a complete recovery?

DR. HOLINGER.—Death is usually due to secondary complications. Lipoid infiltration of other organs may prepare the field for such complications as nephritis when the kidney is infiltrated with lipoid. Some patients appear to make an almost complete recovery.

DR. J. V. GREENEBAUM, CINCINNATI.—The prognosis is not always bad. One patient seen by us, aged 1 year, recovered with careful feeding. Two cases have come to autopsy with findings like those in Dr. Holinger's cases.

DR. E. C. DAVIS, CHICAGO.—Most babies starting cod-liver oil sputter and choke a lot. How long should one persist in attempting to get the infant to take cod-liver oil?

DR. MUNNS.—Cod-liver oil should be started in very small doses and increased very gradually. If the child objects very much, a concentrate should be used.

DR. NICHOLSON.—This condition usually follows the constant use of these oils rather than the large single amounts.

DR. P. C. ELLIOTT, NASHVILLE.—I know the case of a child who developed lipoid pneumonia after only one or two doses of mineral oil.

DR. VAN ORDER.—Does iodized oil ever cause lipoid pneumonia?

DR. HOLINGER.—I have seen no cases as yet due to iodized oil. This oil is a saturated vegetable oil which is less irritating than mineral oil.

DR. J. J. POLLACK, DETROIT.—Is the use of lipiodol with the bronchoscope a safe procedure?

DR. HOLINGER.—Yes. However, diagnostically and therapeutically, other methods of injecting it have proved much more satisfactory.

DR. GOLDBLOOM.—All oils are not the same. The population of Montreal is four-fifths French. Their practitioners come largely from the French schools. They use a nose drop of gomenol oil from early infancy and often over long periods of time. What is gomenol oil?

DR. HOLINGER.—It is an oily liquid used as an antispasmodic.

DR. CLARK.—Does the aspiration of barium following a barium meal in children, which is occasionally followed by vomiting, ever cause pneumonia? Would there be a medicolegal angle to this?

CHAIRMAN ABT.—This would be theoretically possible, but personally I do not know of any such case.

DR. HOLINGER.—In this second portion of the discussion of the nontuberculous chest, Dr. Abt suggested that we discuss the pulmonary findings of certain conditions whose fundamental pathology is dependent upon bronchial obstruction. The three stages of obstruction manifest themselves by a wheeze, obstructive emphysema, and an atelectasis as the obstruction increases in its severity. These types of obstruction are exhibited most characteristically when a foreign body is aspirated into the tracheobronchial tree, and our slides, using foreign bodies to illustrate these phases of obstruction, show the mechanical changes in the lung which take place.

The first subject we wish to discuss in relation to bronchial obstruction is that of a sequence of inflammatory bronchial stenosis which produces an atelectasis, and finally, if the atelectasis persists for a period of months, development of a bronchiectasis in the atelectatic area.

CHAIRMAN ABT.—In the bronchiectasis, regardless of cause, we must presuppose some weakening of the bronchial wall. After atelectasis or bronchopneumonia, there is later fibrosis or obstruction. What is the influence of the pressure of retained secretions on the formation of bronchiectasis?

DR. HOLINGER.—The pressure has not been considered as important as the type of infection, I believe.

CHAIRMAN ABT.—Is weakening due to degeneration of some tissue?

DR. HOLINGER.—It seems to be the elastic tissue.

DR. H. K. TENNEY, MADISON, WIS.—What is the relation of upper respiratory infection, as, for example, sinus infection?

DR. VAN ORDER.—Bronchiectasis is sometimes due to chronic sinus infection resulting from postnasal drip, especially at night. Posture might be important here.

DR. HOLINGER.—Sinusitis may light up bronchiectasis, and advanced bronchiectasis is always accompanied by sinus infection. The early cases do not always have an accompanying sinusitis. Postural drainage, especially before meals, is a very important adjunct to therapy. This lessens coughing and vomiting at meals. Early morning postural drainage is especially important.

DR. STORTS.—In most of our cases of sinusitis, there is a familial history of the condition. The question of the allergic origin of sinusitis is very important. Sinusitis is sometimes due to fungus infection, but whether this is primary or secondary is often not known. We feel that our climate helps more than our doctors. I employ postural drainage for bronchiectasis, sometimes as often as every hour. A wide abdominal belt has been found useful in patients who cough a lot. We employ a high vitamin diet, iodine therapy, neoarsphenamine, bronchoscopic treatment, and operation when necessary.

DR. CHESNEY.—What about sun baths in the desert?

DR. STORTS.—We employ sun baths in the summer but not in the winter.

DR. S. J. HOFFMAN, CHICAGO.—Is there any objection to the use of sunlight in the treatment of bronchiectasis?

CHAIRMAN ABT.—I do not know of any. There is some question as to whether there is a congenital form of bronchiectasis. Some of the cases formerly de-

scribed were probably congenital lung cysts. How frequently is congenital bronchiectasis seen, if there is any such thing?

DR. GREENEBAUM.—I do not know but I have seen congenital cysts of the lung.

DR. CHESNEY.—How important is whooping cough as an etiological factor in bronchiectasis?

DR. HOLINGER.—A large percentage of cases give a history of having had whooping cough and measles at about the same time, and the onset of symptoms of bronchiectasis date from that time.

CHAIRMAN ABT.—In both measles and whooping cough, pneumonia is a common complication. This type of pneumonia may result in a prolonged interstitial involvement. The same is true of a "grippe" pneumonia. A bronchiectasis presupposes a degeneration and weakening of the bronchial wall. Some use postural treatment.

DR. TENNEY.—My opinion is that the continued postural treatment is no better than the commonly employed interrupted treatment.

DR. H. R. ROEHM, BIRMINGHAM, MICH.—What do you think of postural treatment during unresolved pneumonia?

DR. HOLINGER.—True unresolved pneumonia is a relatively rare condition. More frequently the failure of actual resolution is due to an atelectasis with obstructing secretions; consequently, in such a case postural drainage would be indicated very definitely; whereas, in true unresolved pneumonia I believe it would be of little benefit.

DR. ROEHM.—At the University of Michigan, we operated upon a subpleural abscess following an atelectasis which cleared up.

DR. GREENEBAUM.—Do you advise lobectomy?

DR. HOLINGER.—Yes, thoracic surgeons have improved the technique in recent years to give brilliant results in otherwise hopeless cases.

DR. CLARK.—Is x-ray therapy of any value in bronchiectasis?

DR. HOLINGER.—It is used. We have not had good results with it.

DR. POLLACK.—X-ray therapy in atelectasis with marked enlargement of the hilus glands may be useful.

DR. C. K. STULIK, CHICAGO.—One must be certain to rule out tuberculosis, for under this treatment an old tuberculous lesion will flare up.

DR. GOLDBLOOM.—We had a total pneumonectomy in a 10-year-old child who later was reported well.

DR. G. L. BRENNAN, JACKSONVILLE, ILL.—I had a patient with a primary obstruction in the larynx. On three occasions Dr. Arbuckle of St. Louis was able to abort a pneumonia in this patient by aspirating the lung. Early aspiration of the lung prevents lung disease.

DR. POLLACK.—What is your method of instilling lipiodol?

DR. HOLINGER.—The child is placed on the bronchoscopic operating table just as before any bronchoscopic procedure. No anesthetic is used; morphine may be given beforehand to reduce the cough reflex. A catheter is passed through the

nose and into the hypopharynx. It is guided into the larynx and trachea by means of laryngeal forceps after the larynx is exposed with the laryngoscope. Then under the fluoroscope the catheter is manipulated into the particular main bronchus to be visualized, and the oil is instilled through the catheter under fluoroscopic guidance. In older children one or two cubic centimeters of larocain or pontocain is instilled into the catheter prior to the oil. This reduces the cough reflex. The picture is taken immediately.

DR. E. R. McCLUSKEY, PITTSBURGH.—Does congenital narrowing of the bronchi ever occur?

DR. HOLINGER.—Congenital stenosis of a bronchus may occur.

DR. M. W. POOLE, DETROIT.—How long should one wait before starting bronchoscopy?

DR. HOLINGER.—The bronchoscope is a speculum. If an atelectasis is present for a few days and no etiology is apparent, then certainly the tracheobronchial tree should be inspected whenever conveniently possible.

DR. POOLE.—If following pneumonia, how long should it be watched?

DR. HOLINGER.—If symptoms of atelectasis or so-called unresolved pneumonia persist after an acute upper respiratory infection despite the use of postural drainage and expectorants, bronchoscopy seems indicated within from ten days to two weeks, depending upon the degree of involvement and the child's general condition. The relationship of these so-called unresolved pneumonias to atelectasis and bronchiectasis has been so important in our experience that it cannot be overemphasized. This is actually a prebronchiectatic stage, and every effort should be made not to overlook the dullness, râles, bronchial breathing, and chronic cough that persist after the atypical pneumonias which are so frequently associated with upper respiratory disease in children.

Asthma

DR. HOLINGER.—Jackson's old adage, "All is not asthma that wheezes," expresses very clearly the bronchoscopic phase of the diagnosis of asthma in childhood. A wheeze is produced by a partial bronchial obstruction or tracheal obstruction which, in turn, may be produced by a foreign body, pressure of a tuberculous gland upon the bronchial wall, any type of bronchial stenosis, or, finally, a plug of mucus with the characteristic redundant mucosal walls that are seen in the true asthmatic patient. We are particularly interested now in this latter type of patient. The asthmatic child is bronchoscoped in order to make a differential diagnosis between the conditions mentioned above. Then, too, the secretion is aspirated, the morphology determined, and a bacteriologic study made. A vaccine is prepared from this material, and occasionally it gives some benefit. Therapeutically, the bronchoscope is used to aspirate mucus plugs which obstruct the bronchi and give symptoms of acute respiratory embarrassment in some instances. The most extreme instance of this nature that we have observed was seen in a 10-year-old boy who developed a complete atelectasis of the left lung during an asthmatic attack. A foreign body was suspected although the history was negative. The child was bronchoscoped, and the bronchus was found completely obstructed by thick, viscous mucus. Aspiration of this material was followed by a rapid reaeration of the lung, but the child had a complete recurrence on two subsequent occasions at six-month intervals. Smaller areas of atelectasis occur more frequently; generally the mucus plug is coughed out. However, if relief is not obtained within a relatively short time, bronchoscopy seems indicated.

DR. WILLIAMS.—Is there any more danger in bronchoscopy in the asthmatic patient?

DR. HOLINGER.—No, I believe there is no danger in bronchoscopy in an asthmatic patient for diagnosis and therapy if the indications for this procedure are present. By that I mean that the indications must be weighed against the contraindications, taking into consideration the actual purpose of the procedure in the particular case in question and what one expects to accomplish. A bronchoscopy in a child having a marked asthmatic type of breathing would be definitely contraindicated, for example, if it could be shown by x-ray that the asthmatic type of breathing was produced by an enlarged thymus compressing the trachea.

DR. GOLDBLOOM.—If we look well enough and far enough for the cause, the condition will prove not to be the thymus as suspected but something more logical. The thymus may not possibly compress the trachea or vessels.

CHAIRMAN ABT.—I think every organ at times may produce pressure. What about, for instance, a thymoma or cyst?

DR. GLASER.—Thus far I have experienced no cases of asthma in which I have had occasion to consult a bronchoscopist. The children are either so ill that it would be too dangerous to bronchoscope them or not ill enough for bronchoscopic intervention.

DR. HOFFMAN.—What is the relationship between upper and lower respiratory infections and bronchial asthma?

DR. GLASER.—The usual bronchial asthma represents a stage in the evolution of the allergic person who typically was a colicky baby, later developing eczema and then recurrent upper respiratory infections, followed by hay fever or asthmatic bronchitis and then asthma.

Postoperative Pulmonary Complications

DR. HOLINGER.—Postoperative pulmonary complications present such a variety of problems that, for the sake of clarity, we shall limit the discussion to cases in which there is a definite intrabronchial obstruction. In studying these cases, we find they represent the majority of all postoperative pulmonary complications. The nature of the obstruction may vary, but the ultimate result, if the obstruction is not relieved, is always the same, namely, atelectasis and suppuration beyond the point of obstruction. The therapy in these cases must be directed toward relieving the bronchial obstruction and releasing the secretions which have formed beyond it, thus establishing drainage to the infected areas. The first of these conditions, postoperative massive collapse of the lung or postoperative atelectasis, is one which has been of increasing interest to the bronchoscopist. Lee, Tucker, Jackson, and others first demonstrated the dramatic relief to be given by bronchoscopic aspiration of the obstructing secretions. It is not to be confused with postoperative pneumonia since the therapy of pneumonia is exactly opposite to that of the treatment for atelectasis.

There are several important etiological factors which I would like to stress. Morphine and other sedatives, both preoperatively and postoperatively, so reduce the threshold of the cough reflex that secretion lies in the tracheobronchial tree and is not expelled by the bechic blast. Similarly, secretion in the bronchioles is not forced into the bronchi by the tussive squeeze. Previous chest pathology, such as a chronic bronchitis, is certainly a factor in producing increased amounts of secretion. Similarly, a long preoperative stay in bed may result in retained secretions. Preoperative atropine makes this secretion thicker and more tenacious, gumming the

cilia so completely that they cannot perform their function. There is much discussion as to whether the type of anesthetic plays a role. Apparently it does not.

Postoperatively certain factors are of great importance from a prophylactic, as well as a therapeutic, point of view. The common practice in recent years of hyperventilating the lungs immediately on completion of the anesthetic seems to be of utmost benefit. The use of carbon dioxide and postural changes every two or three hours, day and night, should some chest symptom suggest itself, is definitely indicated. Certainly the use of carbon dioxide is of more value than the administration of oxygen, because the carbon dioxide stimulates more active respiratory action, which tends to displace the obstructing secretion. Oxygen, on the other hand, allows the patient to obtain the same amount of pulmonary exchange on shallower respiration. Obviously this is to be avoided, but the administration of oxygen to a dyspneic, cyanotic patient is too frequently the first step taken, and unfortunately it seems too rational to stand criticism. The use of a tight abdominal binder, especially in a case of an upper abdominal operation, further limits the respiratory excursions and increases the incidence of collapse.

The first symptoms usually occur from twenty-four to forty-eight hours after the operation, beginning with chest pain and a persistent, somewhat productive cough which the patient attempts to suppress, both because of the pain at the site of the incision and the chest pain. Respiration becomes shallower and more rapid, soon becoming definitely labored. This may progress to cyanosis. There is a correspondingly rapid rise in temperature, but the pulse rate does not rise proportionately. The sputum at the onset is scanty; it is thick, tenacious, usually glossy or white, and only later becomes purulent.

Physical findings, essentially, are the shift of the heart and mediastinum to the affected side, dullness, limitation of motion, and elevation of the diaphragm. Breath sounds change rapidly, depending upon the amount of obstruction and whether a coughing spell dislodges secretions. They may be entirely absent, suppressed, or bronchial in character, depending upon whether partial or complete atelectasis exists.

The roentgenologic findings are of greatest importance, and these can be demonstrated to best advantage by the films themselves.

The picture described in the textbooks of a plug of mucus in a bronchus does not give adequately the bronchoscopic findings in most cases. On introduction of the bronchoscope through the larynx, one is impressed by the tremendous amount of secretion lying in the trachea and both bronchi. Because of its viscosity, it is aspirated with difficulty; but, by using an aspirating bronchoscope and an independent aspirator, one is able to aspirate more secretion in a minute or two than the patient can cough up in several days. The secretion, if the aspiration is done shortly after the onset of the collapse, is white, very thick, viscid, and tenacious, and it usually clots when it gets into the collecting tube. It contains a great deal of fibrin, but very little pus or bacteria.

The character of the mucous membrane also depends to a great extent on the length of time between onset of the collapse and bronchoscopy. Early there is surprisingly little change in the mucous membrane; only a slight edema and inflammation are found. The entire bronchoscopic picture changes, however, if the bronchoscopy is done later in the course of the disease. The secretion becomes purulent and foul-smelling because it has been an excellent culture medium for organisms. After aspiration the bronchial wall is found to be intensely inflamed and edematous. Secondary bronchial orifices occasionally are closed entirely by the edema. A purulent bronchitis has developed, which may go on to lung abscess or bronchiectasis, or the case may terminate fatally as the patient drowns in his own secretions.

The change in the general condition of a patient following bronchoscopic aspiration is often as striking as that seen following tracheotomy. The immediate relief is reflected in the temperature, pulse, and respiration curves. Physical findings and roentgenologic examination show a rapid return to normal, although the cough continues to be productive for a few days. Should there be a tendency to replugging, however, one need not hesitate to repeat the bronchoscopic aspirations.

One frequently hears that these patients will get well without specific treatment. This is not always true. In any case, however, after the correct diagnosis is made, sedatives should be withheld, the position of the patient changed repeatedly, and carbon dioxide used. Bronchoscopic aspiration, when these methods fail, will hasten convalescence and prevent the more destructive pulmonary complications for which the prognosis is much more grave.

CHAIRMAN ABT.—What is the difference between massive collapse and atelectasis? May I answer by saying that there is no essential difference; atelectasis is a condition where the lungs retain their fetal type and have never really expanded; whereas, by collapse is meant an acquired atelectasis in a lung which was once expanded. Collapse may occur after abdominal surgery, notably after appendectomy. It is due to the aspiration of mucus and plugging of a main bronchus.

DR. HOFFMAN.—I recently saw two cases of lobar pneumonia following a tonsil and an adenoid operation in the same week; both recovered. Could this have been due to the operation?

DR. HOLINGER.—I should think that would be pretty difficult to answer if they were true pneumonias.

DR. T. P. SALTIEL, CHICAGO.—Is x-ray the only evidence in diagnosis?

DR. HOLINGER.—No, the history and physical findings are usually characteristic enough so that the diagnosis may be made without x-ray. The position of the heart and the dullness and elevated diaphragm on the involved side are generally easily recognized physically.

DR. ANDREWS.—How long after the operation before interference with respiration is noted?

DR. HOLINGER.—It may be noted within a few hours and only rarely occurs after forty-eight hours.

DR. GOLDBLOOM.—Is there any reason to delay?

DR. HOLINGER.—None.

CHAIRMAN ABT.—When then would you operate?

DR. HOLINGER.—I believe the time of operative intervention must be judged by the clinical course of the case. If the child is extremely dyspneic, the aspiration should be done without delay. In a milder case, the simpler procedures, such as CO_2 inhalations and frequent turning, could be tried first, and if these fail to bring relief and reaeration of the lung, the indication for bronchoscopy would be clear.

DR. GREENEBAUM.—In an infarct of the lung, bronchoscopy is not used.

DR. R. E. CUMMINGS, CHICAGO.—At how young an age may a baby be safely bronchoscoped? We had one 10 months old with a piece of bacon in the bronchus, and he was safely bronchoscoped. Are they more apt to have trouble following the procedure than the older children are?

DR. HOLINGER.—A baby of any age may be safely bronchoscoped by a well-trained team if a bronchoscope small enough to pass easily through the larynx is used. We had a 24-hour-old baby with marked obstructive emphysema due to a congenital bronchial cyst. It developed no postoperative laryngeal edema and made an uneventful recovery. It is essential to limit the procedure to as short a time as possible.

Interstitial Pneumonia (Fibroid Pneumonia)

CHAIRMAN ABT.—This condition is not to be confused with tuberculosis. It follows some acute pulmonary infection; it may be a sequel of bronchopneumonia, rarely of true lobar pneumonia. It is called unresolved or protracted pneumonia and was described by the early English physicians. Bronchiectasis is not an uncommon sequel. Kyphoscoliosis has been observed, and retraction or flattening of the thorax is frequent. The area involved may be small. On the other hand, it may involve a whole lobe or lobes. It occurs in infancy and may persist until adult life. The life span of these patients is usually short, and malnutrition with emaciation is progressive.

DR. H. A. SLESINGER, WINDBER, PA.—Fungus infection may be a secondary invader. In one such case, 500 grains of the iodides daily brought about a cure.

SUMMARY

Laryngotracheobronchitis is an acute, inflammatory process occurring with a croupy cough, a cold, and a gradually rising temperature. It is ordinarily seen in a child under 2 years of age.

Embarrassment of respiration and even death may occur from the obstruction to breathing from the thickened mucosa and the accumulation of ropy mucus. The organisms usually found on culture of the secretions are the staphylococcus and the streptococcus. The pathology is that of a streptococcus infection.

The treatment consists of maintaining the body fluid balance and nutrition, building up resistance, and keeping the air passages sufficiently open to supply adequate oxygen and thus afford necessary rest. Early in the treatment, if one is suspicious of a laryngeal diphtheria, antitoxin should be given.

To maintain an open airway, the patient is kept in a room at 74 to 76° F. with humidity over 90. This makes the secretions less tenacious. Some use a cold room with outside air, but generally the warm one is more suitable to the patient. Oxygen spares respiratory effort and is useful.

When these measures are not sufficient, bronchoscopy to remove secretions and, at times, tracheotomy are indicated. Intubation is not usually adequate. The expectorants are of only slight value; sedatives are sometimes useful. Atropine and opium are not advised.

Lipoid Pneumonia.—This condition has been observed occasionally after the continued use of oily nose drops or mineral oil or cod-liver oil by mouth.

It is a chronic disease characterized by a low-grade fever, cough, wasting, and a bizarre x-ray film showing the pathology principally in the upper lobes. The above, plus the finding of oil in the sputum or in specimens obtained on bronchoscopy, makes the diagnosis. The prognosis is grave; death is usually due to a superimposed infection. A few patients recover after a long illness. General measures to build up resistance and nutrition are employed.

Bronchial Obstruction.—In obstruction following the aspiration of a foreign body, the pathology is first a wheeze, then emphysema, atelectasis, and bronchiectasis.

Bronchiectasis frequently complicates measles and whooping cough. Atelectasis is observed following pneumonia, and these patients should be bronchoscoped early to determine the condition of the lung. Bronchoscopic examination may be safely carried out, even in the very young.

Atelectasis at times complicates true bronchial asthma, a mucous plug blocking a bronchus. The bronchoscopist removes this, with early relief. A relationship does exist between asthma, sinus infection, and allergy.

Massive collapse of the lung following surgical procedures should be recognized, since early bronchoscopy with removal of the obstruction is the only means of a speedy recovery. The symptoms are pain, cough, characteristic sputum, and x-ray evidence of a shift in the position of the heart. If not treated early, a purulent bronchitis, perhaps followed later by an abscess of the lung or bronchiectasis, develops.

TREASURER'S REPORT

STATEMENT OF RECEIPTS AND DISBURSEMENTS
JULY 1, 1939, TO JUNE 30, 1940

Balance, July 1, 1939				$10,283.21
Receipts:				
Dues			$25,160.25	
International Congress of Pediatrics			5,980.00	
Exhibits, 1939 Meeting		$2,665.00		
Exhibits, 1940 Meeting		2,062.50	4,727.50	
Interest			603.18	
Pamphlets, Child Health Record			90.70	
Immunization Procedures			283.10	36,844.73
				$47,127.94
Disbursements:				
International Congress of Pediatrics			$ 6,060.00	
Salaries:				
Secretary	$7,500.00			
Stenographer	2,000.00			
Office	525.00	$10,025.00		
Rent		1,000.00		
Subscriptions		6,450.70		
Publicity		3,802.10		
Annual Meeting, 1939	$3,276.46			
Annual Meeting, 1940	18.00	3,294.46		
Executive Board		2,544.43		
Printing and Stationery		809.26		
Postage		675.00		
Traveling Expense		530.55		
Deposit, Air Lines		425.00		
"Child Health Record"		389.51		
Office Supplies		220.66		
Refunds, Initiation Fees		125.00		
Exchange and Charge on Checks		93.45		
Treasurer's Bond		62.50		
Telephone and Telegrams		35.09		
Certificates		24.80		
Miscellaneous		92.01		
Regional Expense:				
Region I	$ 217.00			
Region II	90.86			
Region IV	8.48	316.34		
State Expense		452.29		
Committees:				
Child Health Relations	$ 100.00			
Contact Infections	194.55			
Honorary Fellowships	5.10			
Immunization Procedures	292.30			
Medical Supervision of Camps	14.15			
Mental Hygiene	23.00			
Nonmedical Groups	161.02			
Problems of the Fetus, etc.	31.85			
Scholarships	5.70	827.67	32,195.82	38,255.82
Balance, June 30, 1940				$ 8,872.12

ANNUAL MEETING, REGION I OF THE AMERICAN ACADEMY OF PEDIATRICS

WASHINGTON, D. C., APRIL 4, 5, AND 6, 1940

The scientific sessions of the annual meeting of Region I in Washington, D. C., were opened with addresses by Dr. Thomas Parran, Surgeon General of the United States Public Health Service, and Dr. Martha M. Eliot, Assistant Chief of the Children's Bureau, United States Department of Labor. The program was opened with a discussion of the vitamin B complex by Dr. William H. Sebrell, who is in charge of investigations relating to nutrition in the National Institution of Health, and by some of the physicians associated with him in various phases of the research. Vitamin B complex is composed, said Dr. Sebrell, of between ten and fourteen different factors; how many it is not known definitely. He showed that some vitamin B deficiencies were recognized as multiple and cited case histories to prove this fact. Dr. R. E. Butler exhibited colored motion pictures showing ulcerations in the corners of the mouth and ulceration with increased secretion of mucus in the nasal mucosa. After the administration of riboflavin, these lesions melted out, as was clearly shown in the pictures. Interstitial keratitis definitely appears to be due to riboflavin deficiency; even known cases of syphilis with interstitial keratitis, resistant to antisyphilitic treatment, have responded favorably to the administration of riboflavin. Dr. Floyd S. Daft discussed what is known about vitamin B_6 or pyridoxine and pantothenic acid, the synthesis of which had been announced a few weeks before.

Two other symposia are worthy of mention. Dr. McLeod and Dr. Branham presented one on meningitis in which they showed that proper treatment of meningococcus meningitis was dependent upon the laboratory for the diagnosis of the type of meningococcus in order to determine its appropriate serum, more particularly if the organism belonged to Type II. Dr. Rice and Dr. Lindsay showed the encouraging reduction of mortality in cases of influenzal meningitis treated with sulfapyridine and Fothergill's serum with added complement. Dr. Charles Armstrong gave an outstanding exposition, from all points of view, of acute benign lymphocytic meningitis. The fourth symposium presenting facts not so well known among pediatrists was that on Rocky Mountain spotted fever. As part of this presentation, a colored motion picture, prepared by United States Public Health Service physicians stationed in Bitter Root Valley, Mont., depicted the "Life History of the Tick," a cycle of development requiring two years; the film required thirty minutes, but those present manifested great interest in it.

During the three days of the meeting there were four half-day sessions of scientific papers. Besides these, the afternoon of the first day was given over to a panel discussion of types of pediatric service and factors influencing the quality of medical care in the various types. This session ended with a question period, in which many written queries were sent up from the floor and assigned to various members of the panel by Chairman Stanley Nichols.

There were eighteen scientific exhibitions demonstrating papers in the program. The Friday morning session was followed by clinical demonstrations of patients.

The medical staff of the Children's Bureau entertained the state chairmen of Region I at dinner at the Admiral Club. The opportunity for free and informal discussion of their common problems and interests as well as differences of opinion, seemed to be appreciated, and the discussion extended until midnight.

The entire community was interested in the purposes and success of the meeting, and everyone capable of contributing did so willingly. A spirit of friendliness and

cordiality pervaded the meeting. Many research workers who were nonmembers of the Academy gave freely of their time to prepare and present papers and to prepare and demonstrate scientific exhibits.

There were 225 Fellows and 205 physician guests who registered. Over 500 Fellows and guests attended the dinner on the evening of the first day, and over 800 went to the White House Reception arranged through the courtesy of Mrs. Franklin D. Roosevelt.

HARRY H. DONNALLY.

Academy News

The 1941 Regional Meetings of the American Academy of Pediatrics are scheduled as follows:

Region I—New Haven, Conn., March 28 and 29.
Region II—Richmond, Va.
Region III—Palmer House, Chicago, Ill., May 15, 16, and 17.
Region IV—San Francisco, Calif.

The Academy has recently issued a "Child Health Record" from infancy to adulthood, which has been distributed to the members. The book contains material for important data regarding the child's growth and development, immunizations, illnesses, etc. The "Child Health Record" is supposed to be a given child's record to be kept by the parents, with the notations made and kept up to date by the physician. Some minor changes will be made in the next printing. The record is attractively printed and will serve a very useful purpose. Additional copies may be obtained through the secretary's office in Evanston.

Dr. Hugh L. Dwyer, Kansas City, has been made Health Commissioner of Kansas City.

News and Notes

The following physicians have been certified by the **American Board of Pediatrics** since the last report:

Dr. Mary Adams, Riverside, Conn.
Dr. Horst Albert Agerty, Merion Station, Pa.
Dr. Lawrence Charles Bachmann, Pittsburgh, Pa.
Dr. W. Warrick Cardozo, Washington, D. C.
Dr. Alice Drew Chenoweth, Rosemont, Pa.
Dr. Elizabeth Chickering, Washington, D. C.
Dr. J. Wallace Cleland, Lansdowne, Pa.
Dr. Richard L. Day, New York, N. Y.
Dr. Robert H. Detwiler, Arlington, Va.
Dr. Richard A. Downey, Buffalo, N. Y.
Dr. Herbert L. Elias, Rockville Center, N. Y.
Dr. H. H. Finlay, Wilkinsburg, Pa.
Dr. S. Howard Fleri, Brooklyn, N. Y.
Dr. John Edward Franklin, New York, N. Y.
Dr. Emily Gardner, Richmond, Va.
Dr. Milton M. Greenberg, Washington, D. C.
Dr. Isaac F. Gittleman, Brooklyn, N. Y.
Dr. Moe Goldstein, Forest Hills, Long Island, N. Y.
Dr. James P. Hanner, Atlanta, Ga.

Dr. Edward Harshaw, Jr., Yeadon, Pa.
Dr. William Allen Howard, Washington, D. C.
Dr. Betty Huse, Washington, D. C.
Dr. Margaret Holden Jones, Cheyenne, Wyo.
Dr. Isaac W. Karlin, Brooklyn, N. Y.
Dr. Louise M. Kochin, Pittsburgh, Pa.
Dr. Arthur Lesser, New York, N. Y.
Dr. Joseph L. Lewis, Boston, Mass.
Dr. Harry Lowenburg, Jr., Philadelphia, Pa.
Dr. Rocco J. Martoccio, Utica, N. Y.
Dr. Paul Francis McAlenney, Jr., New Haven, Conn.
Dr. Jean McAlister, Greensboro, N. C.
Dr. Robert A. Moore, Charlotte, N. C.
Dr. Gertrude Halero Brown Nicolson, New York, N. Y.
Dr. Edward Thomas O'Donnell, Wilmington, Del.
Dr. Jean Pakter, New York, N. Y.
Dr. John Robert Phillips, Allentown, Pa.
Dr. Jacob David Pinson, Philadelphia, Pa.
Dr. Howard G. Rapaport, New York, N. Y.
Dr. Henry Rascoff, Brooklyn, N. Y.
Dr. Harold A. Rosenberg, Jackson Heights, Long Island, N. Y.
Dr. Isadore Rosmovsky, Staten Island, N. Y.
Dr. Eli Rubenstein, Bayonne, N. J.
Dr. Michael Schuman, New York, N. Y.
Dr. Myron Ezra Wegman, Baltimore, Md.
Dr. Samuel Bernard Weiner, New York, N. Y.
Dr. Louis Ernest Weymuller, New York, N. Y.
Dr. Henry Booth Wightman, New Rochelle, N. Y.
Dr. Abbott L. Winograd, Nashua, N. H.
Dr. C. Michael Witzberger, New York, N. Y.
Dr. Charles Louis Wood, New York, N. Y.
Dr. Tyree C. Wyatt, Syracuse, N. Y.
Dr. Russell John Blattner, St. Louis, Mo.
Dr. James Meredith Coleman, Austin, Texas
Dr. James Joseph Donahue, East St. Louis, Ill.
Dr. Lucius Elkanah Eckles, Topeka, Kan.
Dr. Gerald Robert Fisher, Colorado Springs, Colo.
Dr. C. Dixon Fowler, Atlanta, Ga.
Dr. Robert Clarence Fredeen, Kansas City, Mo.
Dr. George V. Herrman, Kansas City, Mo.
Dr. L. Martin Hardy, Chicago, Ill.
Dr. Robert Lawrence Jackson, Iowa City, Iowa
Dr. F. Craig Johnson, Denver, Colo.
Dr. Haddow M. Keith, Rochester, Minn.
Dr. Bruce A. Knickerbocker, Dallas, Texas
Dr. George Maksim, Petoskey, Mich.
Dr. Kenneth W. A. McLeod, Lapeer, Mich.
Dr. Donald Norman Medearis, Kansas City, Kan.
Dr. Ernst R. Moeller, Denver, Colo.
Dr. Louis S. Robins, Chicago, Ill.
Dr. Arthur H. Rosenblum, Chicago, Ill.
Dr. Isadore B. Silber, Cleveland, Ohio
Dr. Joseph McBride Sloan, Corpus Christi, Texas
Dr. Charles A. Tompkins, Omaha, Neb.
Dr. Simon A. Wile, Chicago, Ill.
Dr. Herbert C. Archibald, Salinas, Calif.
Dr. Sherod Marshall Billington, Seattle, Wash.
Dr. Edwin Revere Cole, Sacramento, Calif.
Dr. William C. Deamer, San Francisco, Calif.
Dr. Scott H. Goodnight, Portland, Ore.
Dr. Frederick R. Fischer, Spokane, Wash.
Dr. Margit Helga Grytbak, Seattle, Wash.
Dr. Helen Hopkins, Los Angeles, Calif.
Dr. Frederick B. Joy, Seattle, Wash.
Dr. Pearl Vivian Konttas, Santa Rosa, Calif.
Dr. Robert Spencer Leet, Oakland, Calif.
Dr. Robin M. Overstreet, Eugene, Ore.
Dr. Karl Francis Pelkan, San Jose, Calif.
Dr. Willard B. Rew, Yakima, Wash.
Dr. Leslie A. Smith, Ogden, Utah
Dr. Frank Marion Sprague, Boise, Idaho
Dr. H. Milton Van Dyke, Long Beach, Calif.
Dr. Leon Z. Wolpe, Los Angeles, Calif.
Dr. Charles Andrew Wylie, San Bernardino, Calif.

The **American Board of Pediatrics** announces the following examinations in 1941:

March 30 and 31, 1941—New York, N. Y. (following the meeting of Region I of the American Academy of Pediatrics).

May 18, 1941—Chicago, Ill. (following the meeting of Region III of the American Academy of Pediatrics).

Book Review

Graduate Medical Education. Report of the Commission on Graduate Medical Education. Chicago, 1940, University of Chicago Press. Pp. 304.

This is an extensive report on graduate medical education by the Commission organized in December, 1937, as a result of an action by the Advisory Board for Medical Specialties. Dr. Willard C. Rappleye is the chairman of the Commission, which is made up of twenty members, all of whom are associated with medical teaching. Dr. Robin C. Buerki was the Director of Study. The Commission's work was financed by gifts from several foundations and contributions from organizations interested in the problem.

After an introductory "Summary," Chapter II takes up the subject of the internship. This, the report concludes, should be considered as a basic preparation for general practice and should give experience in internal medicine, pediatrics, obstetrics, minor surgery, and surgical diagnosis. It should round out the medical school course and should be closely allied to the undergraduate medical education. It should not include detailed training of the techniques of the specialties. Many subjects such as length of service, staff supervision, and the like are discussed.

Next comes an exhaustive report on "The Residency," a period of prolonged study in one of the special fields. This is properly graduate education, and the service should be considered essentially as educational. The report supports the recommendation of the various specialty boards that adequate attention be given to basic training as related to the specialty. This is a problem by no means solved from a practical standpoint, and the recommendations of the report are necessarily rather vague in this connection. Attention is called to the danger of developing too many residencies, and the report quite correctly considers the present problem one of the quality of teaching rather than of an increase in number. So far as pediatrics is concerned, the importance of the growth and development of the child is stressed. From tables in the appendix we note that the number of physicians limiting their work to pediatrics increased from 689 in 1923 to 2,205 in 1938 (or 22 per cent). Mortality tables show an expectancy of sixty-six deaths per year for the 2,205 pediatricians. This figure is high at the present time, as the age distribution of pediatricians is greatest in the 30- to 40-year decade. There are over 300 residencies in pediatrics now available for training, which would mean 150 newly trained men each year with a residency of two years as required at present, or 100 a year with a three-year residency as required by some boards for certification. The number of certificates issued by the Pediatric Board is greater than the figure given in the appendix table of the report. The figures as of July 1, 1940, are 1,562.

A section is then given to a discussion of postgraduate education, short intensive courses for the general practitioner and the specialist. A chapter follows on the effect of the work of the specialty boards on medical practice and education. The report concludes with an appendix containing pertinent tables and outlines of various postgraduate courses.

The report may be regarded as compulsory reading for all engaged in medical teaching, particularly those on hospital staffs where interns and residents are receiving their education and training. There is no question but that graduate medical education has taken a definite trend in the last decade which is of vast importance, not only as regards the educational content, but also in the structure of medical practice, which will be reflected in improved medical care of patients.

B. S. V.